Division of Research Services

FY 1988 Annual Report

National Institutes of Health

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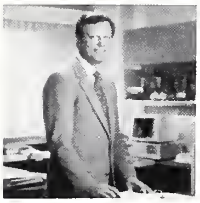

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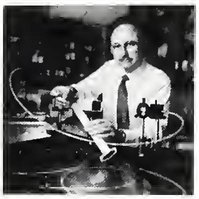

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A Letter From the Director

Robert A. Whitney, Jr., D.V.M.
Director
Division of Research Services
National Institutes of Health

During the past year, DRS has continued its Division-wide productivity and quality review to improve our overall performance in the four Branches and the Office of the Director. We have found that as NIH changes, we must rapidly mirror that change in order to effectively support the intramural research being performed: providing researchers with what they need, when they need it.

We anticipate implementing several changes within our organization during FY 1989 that will help us improve planning capability throughout the Division. Several of these changes will provide significant cost savings to the NIH, allowing a more effective directing of resources towards research activities.

The Division continues to review activities that may be contracted out so that FTEs and resources can be used to provide new and innovative services. This trend toward contract support is illustrated by the fact that from 1970 to 1987 the total DRS budget increased by only 75 percent, while the contract dollars have increased by 1144 percent. In addition, DRS FTEs from 1981 to 1987 have decreased by 14 percent, while contractor equivalent FTEs have increased by more than 39 percent. This trend toward increased contractor support will continue to be an integral part of our plans for improving and expanding our services.

The following reports from the four DRS Branches contain many examples of current initiatives to improve their services to the intramural programs of NIH. A sampling: Scientific Equipment Services, Biomedical Engineering and Instrumentation Branch, has initiated and is increasing many steps that reduce maintenance costs for scientific instrumentation and facilitate researchers' acquisition and use of it; the NIH Library has achieved and documented striking productivity increases throughout its operations, and it is also replacing its automated catalog system with one that is more effective, efficient, and easy to use; Medical Arts and Photography Branch is moving to improve its photomicroscopy services with electronic imaging including computer enhancement and evaluation; Veterinary Resources Branch not only is following through on its move from large-scale animal production to supplying holding rooms, procedure rooms, and technical support for investigators' animal research projects, but is also contributing in a number of ways to NIH's drive for accreditation of the entire NIH intramural animal research program by the American Association for Accreditation of Laboratory Animal Care.

BEIB's report primarily reflects the fruitful collaborations of its four engineering sections and three physical science groups with investigators in almost all the Institutes. The introduction to that report this year features microcalorimetry developmental work that greatly speeds operations and increases resolution to heat differences in microcalorimetry--a technique of fundamental importance in biochemistry. The work is done in collaboration with the Laboratory of Technical Development of the National Heart, Lung, and Blood Institute.

The NIH Office of Animal Care and Use (OACU) is not part of DRS, but is supported administratively by the Division. This year staff of our Office of the Director and VRB have given many kinds of help to OACU staff in their

Division of Research Services FY-88 Budget (in thousands of dollars)

Branch	Management	Service & Supply	Total
Veterinary Resources	$6,657	$10,198	$16,855
Biomedical Engineering & Instrumentation	3,854	8,755	12,609
Library	5,666	—	5,666
Medical Arts & Photography	—	7,389	7,389
Sub Total	16,177	26,342	42,519
*Office of Animal Care and Use	757	—	757
Total	$16,934	$26,342	$43,276

*Organizationally assigned to OD/NIH; Administratively supported by DRS activities to maintain the highest standards of care and use of NIH laboratory animals.

During the NIH Centennial and DRS Thirtieth Anniversary celebrations two years ago, DRS adopted the motto "Proud to Serve" to express our belief that support of the NIH intramural research commitment is our highest priority. As a reminder of that belief, we include in this year's annual report photographs of the four DRS employees who in FY 1988 had the longest service records in their respective Branches. Their excellent service, reaching back to the very earliest years of DRS, is a sample of the performance that can be expected in the future from the men and women of DRS.

The Division of Research Services

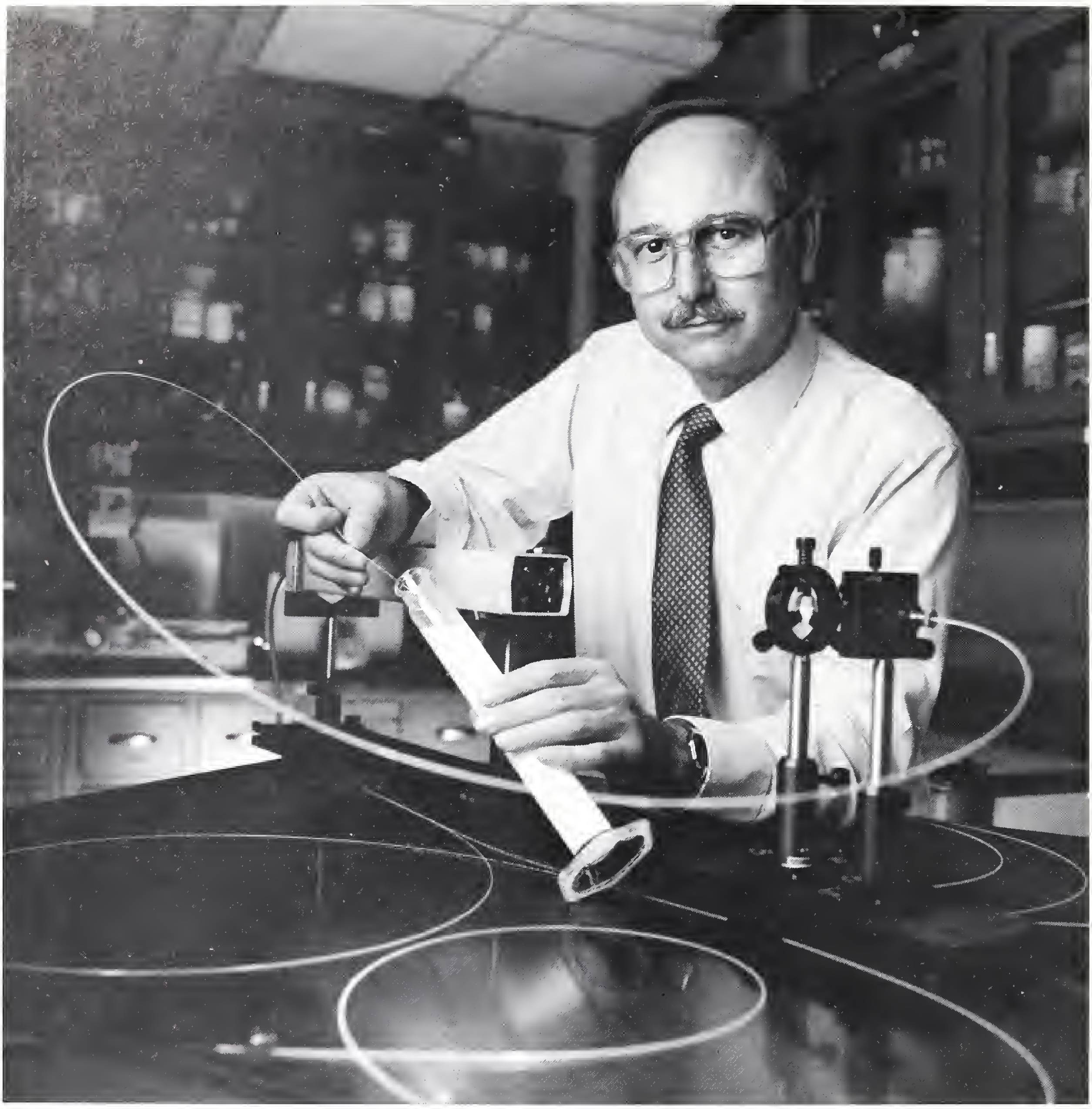
The many specialized functions of the Division are designed to support all of the 20 Bureaus, Institutes, and Divisions (BIDs) that constitute the National Institutes of Health. The primary program emphasis, however, is directed at serving the 8,000 staff members of the intramural program, including more than 2,800 doctoral level scientists who conduct research in NIH laboratories.

Organizationally, the Division is structured to provide products and services in support of the sequential steps in every biomedical research project: planning, making available models and substrates, manipulating and measuring research materials, and recording and communicating research results. Many research projects require the services of all four branches.

- The Library Branch (NIH Library) possesses or has access to virtually all published biomedical information, and its automated systems deliver the information rapidly.
- The Biomedical Engineering and Instrumentation Branch (BEIB) uses engineering, mathematics, physics, and the physical sciences to help NIH investigators solve problems in biology and medicine, especially in measurement, modeling, and design of specialized instrumentation. BEIB also meets a wide range of instrumentation needs including fabrication, modification, maintenance, and repair.
- The Veterinary Resources Branch (VRB) supplies many professional and technical services for the care and use of research animals. Among these are breeding or purchasing needed animals, caring for them skillfully and humanely, and advising researchers on animal health, nutrition, behavior, genetics, reproduction, and care.
- The Medical Arts and Photography Branch (MAPB) meets researchers' visual communication needs by designing and making graphics and medical illustrations, photomicrography and photomacrography, and producing videocassettes of biomedical procedures.

Publications

Whitney RA. U.S. Public Health Service training and career development opportunities for veterinarians. J Am Vet Med Assoc 1988;193:422-7.



John Boretos has been using his expertise in materials science to improve scientific instrumentation in BEIB since 1960. Here he is working on a polymeric coating for a laser catheter used by NCI researchers in photodynamic chemotherapy for esophageal cancer. John developed the special coating to evenly distribute the laser light, which activates a photodynamic treatment agent at the cancer site.

Biomedical Engineering and Instrumentation Branch

Murray Eden, Ph.D.

Advances in Microcalorimetry

Microcalorimetry is the technique of measuring the miniscule amount of heat produced when biochemicals interact. Knowledge of heats of reaction offers insight into mechanisms of interaction between enzymes and substrates, hemoglobin and oxygen, and various drugs and DNA—to give but a few examples.

Traditional "batch" methods of microcalorimetry have been labor intensive and slow. Researchers have had to weigh reagents, load them into reaction vessels, and allow the vessels to equilibrate for several hours, before mixing the reagents and measuring the resulting heat. The cumbersomeness of the process and need to equilibrate for each run limit the number of reactions that can be run to two or three per day. Unfortunately, too, microcalorimeters create mixing artifacts (unpredictable amounts of heat added through stirring) that limit their resolution to heat differences of about 60 microjoules (a microjoule is a millionth of a watt-second).

A three-year collaboration between the Biomedical Engineering and Instrumentation Branch (BEIB) and the Laboratory for Technical Development (LTD), National Heart, Lung, and Blood Institute (NHLBI) has produced a microcalorimeter that overcomes these shortcomings in a spectacular way. The device, called a stopped-flow differential microcalorimeter, eliminates weighing, measuring, and manual insertion of individual samples, long equilibration times, and most mixing artifacts. It can process 120 runs per day with a vastly improved resolution: plus or minus 3 microjoules. Additionally, it requires only 80 microliters of reagent per run, compared to 200 microliters for batch calorimeters, thus conserving scarce materials.

The device achieves its sensitivity through a thermally "differential" mode of operation. That is, it has two identical mixing chambers in which it runs simultaneous tests and compares the results from moment to moment. One chamber receives the reagents of interest; the other receives a control (all the components except the active ingredient). In this way extraneous influences, such as changes in room temperature and mixing, affect both chambers equally and don't lead to differences when the chambers are compared. This well-known engineering principle, known as common-mode rejection, is enhanced by careful thermal matching of components in the two chambers. Thus, while the core temperature of the microcalorimeter may vary as much as one thousandth of a degree centigrade during the course of a day, the difference between the two chambers will vary by only about 5 millionths of a degree.

To achieve high inertness to biological materials, the microcalorimeter is made of the element tantalum. For gas tightness its seams are sealed by electron-beam welding.

Incoming samples automatically equilibrate to the reference temperature through a countercurrent heat exchanger. In this scheme heat from reagents leaving the mixing chambers warms the reagents about to enter.

A microcomputer controls a stepping-motor syringe drive for injection of the samples, eliminating the need for manual measurements. The injection process forces the reagents to flow against each other at high velocity, and the resulting turbulence accomplishes mixing in about half a second. The device completes its measurements in about 150 seconds (compared to 350-450 seconds required for batch methods). The computer records and displays the data.

About three years ago Dr. Robert Berger of LTD, NHLBI, approached BEIB's Dr. Courtney Mudd with the problem of measuring heats of binding between oxygen and hemoglobin as a function of percentage of oxygen saturation of hemoglobin. Dr. Berger wished to make the tests over virtually the entire range of possible oxygen saturations and to do so with a resolution 200 times greater than previously possible. The stopped-flow differential microcalorimeter resulted from this collaboration.

Scientists have devised several models to explain the sigmoid curve of percent hemoglobin saturation vs pO_2. One model postulates a multi-step reaction with binding affinities that change with each step; but no direct experimental verification exists for the model. Drs. Berger and Mudd will use their microcalorimeter to obtain binding heats at various values of pO_2; if there are discrete steps, this would support the multi-step model.

Two years ago Dr. Mudd made a presentation at the International Calorimetry Conference in New Brunswick, New Jersey, on preliminary results of his collaboration. A professor from Rutgers University made arrangements with Dr. Mudd for one of his graduate students to come to NIH to do experiments on the binding of an anti-cancer drug, daunomycin, to DNA.

BEIB's Mission

The Biomedical Engineering and Instrumentation Branch, DRS, is NIH's focal point for engineering and related sciences. Its staff members collaborate with NIH biological investigators in areas where engineering, mathematics, or applied physics can shed light. BEIB's staff are divided into four engineering sections and three physical science groups:

- Applied Clinical Engineering Section
- Chemical Engineering Section
- Electrical and Electronic Engineering Section
- Mechanical Engineering Section

- Analytical Methods Group
- Electron Beam Imaging and Microspectroscopy Group
- Magnetic Resonance Imaging Group.

The major areas of work are:

- Measurement of biological phenomena
- Physical and mathematical models of biological systems
- Design of specialized instrumentation for research and clinical care.

Equally important, the Scientific Equipment Services portion of BEIB operates shops that meet NIH researchers' need for services involving scientific apparatus: design, fabrication, modification, maintenance, repair, and rental services.

By using the new microcalorimeter, the student was able to complete in one month what would have taken two years to do via "batch" methods. Moreover, due to the new device's resolution, he was able to conduct tests of the drug at therapeutic concentrations; previously, he had to use far higher concentrations of the drug in order to produce measurable heat. At higher concentrations, however, daunomycin dimerizes (forms groups of two molecules), making it necessary to guess how the drug would act at therapeutic concentrations. Such guesswork is fraught with problems. Using the new microcalorimeter, the student and his advisor were able to demonstrate that various drugs followed different models. They also produced the first experimental verification that monomeric and dimeric forms of daunomycin have different binding enthalpies (heats). Rutgers has now built its own microcalorimeter, using plans given to them by Dr. Mudd.

In another study with Dr. Berger, the instrument was used to measure the activities of NADH-ase, an enzyme that cleaves a hydrogen ion from NADH. The heat of cleaving is too small to measure directly, so the collaborators amplified the heat by buffering the released ions in a bis-tris buffer and measuring the far-larger heats of titration.

The new microcalorimeter is in such demand that BEIB will build at least one more for use at the NIH. The Center for Biologics Evaluation and Research of the Food and Drug Administration has also requested one.

Drs. Berger and Mudd are contemplating seeking Government patents on their innovations. Plans to refine the device include seeking ways to reduce the priming volumes used by the device, further conserving scarce reagents, and increasing throughput.

BEIB in FY 1988

BEIB has been busy fulfilling its commitment to provide the NIH research community with a broad range of scientific and engineering expertise. BEIB has collaborated in more than 200 projects to produce advanced instrumentation, models, methods, and techniques dedicated to the acquisition of biomedical information previously unavailable to NIH's scientists.

In addition, the staff of approximately 40 physical scientists and engineers and 75 technical support personnel responded to 1400 requests for fabrication or major modification of laboratory devices and nearly ten thousand requests for repairs and minor modifications to scientific equipment.

Status of Current Activities

Over the years, BEIB has initiated several projects that are interdisciplinary in character and do not fit readily within the section structure of BEIB. At present there are three such areas being carried out directly under the administrative control of the Office of the Chief. They are: nuclear magnetic resonance instrumentation, electron beam imaging and microspectroscopy, and microanalytic methods.

Nuclear Magnetic Resonance Instrumentation Group

BEIB continues to explore and support the numerous research opportunities presented by nuclear magnetic resonance, and as the pace of utilization of the *In Vivo* NMR Center has quickened, new challenges have emerged. The question of the safety of the technique has arisen in several instances, particularly when "homemade" surface coils are used by researchers, and the Group has developed two main strategies for assessing and preventing excessive power deposition in patients or laboratory animals. Using resistive paper and a temperature-sensitive, liquid crystal display, the deposition has been dramatically highlighted. Interestingly, the electric fields from several well-known coil designs have been shown to give specific absorption rates that are well in excess of government recommendations.

Once coils are acceptable, there is always the possibility of equipment malfunction, and so simple fuses have been incorporated in their lines (along with the appropriate circuitry to enable satisfactory functioning at radio frequencies) to give very effective "fail-safe" protection.

Another problem being addressed is the deleterious effects of eddy currents induced in the magnet cryostat by rapidly changing field gradients. Thus a program to develop self-shielded, high power gradient coils and solenoids is under way, and with their installation we anticipate that the quality of the 100ms "echo-planar" images being produced on the 4.7T, 40cm bore system will be greatly improved.

Finally, the computing needs of the Center have been met by the VAX facility which, with its array processor and graphics display system, is now fully operational, and a variety of useful programs has been developed. Regrettably, the interconnection of the machine with the NMR instruments has still not been accomplished by the vendor, and this lack has hindered serious attempts at image processing.

Electron Beam Imaging and Microspectroscopy Group

BEIB has continued to develop new microanalytic capabilities and, through collaborations, to apply its computer-controlled analytical electron microscopes to the solution of biological problems. A new high-resolution field emission scanning transmission electron microscope (STEM) is now operational in BEIB and will serve as the principal tool of the Nanometer-Resolution Analytical Facility, a collaborative effort of the National Institutes of Health and the National Institute of Standards and Technology (formerly known as the National Bureau of Standards). The facility also has state-of-the-art sample preparation equipment, including an ultracryomicrotome and a high vacuum freeze-drying/electronbeam evaporation system, that are essential to achieving the full microanalytical capabilities of the STEM.

On May 12-13, 1988, BEIB sponsored a symposium entitled "Frontiers in Electron Microscopy: The Field-Emission STEM." The purpose of the symposium, attended by over two hundred people, was to inform NIH scientists of advances in this technique for applications to high-resolution studies of biological structures. The timing of the symposium coincided with the dedication of BEIB's new field-emission STEM facility.

BEIB has recently added a multichannel parallel detection system to the electron energy loss spectrometer on its older 200 kev STEM, improving its detection efficiency a thousandfold. The detector can produce high-quality spectra in one tenth of a second, making possible real-time electron energy loss spectroscopy.

Preliminary studies involving fluorine analogs of neurotransmitters suggest that BEIB may be able to detect these compounds within cells at biological concentrations. In December 1988 an NRC Research Associate will join the group to work in this important area.

In collaboration with the Laboratory of Neurobiology, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the Group has measured the calcium concentration of dendritic spine organelles in cryofixed mouse cerebellum. The calcium content in the post synaptic spine cisterns was found to increase by a factor of three on stimulation.

In collaboration with the Laboratory of Cell Biology and Genetics, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), studies have continued on the composition of secretory granules in bovine adrenal chromaffin cells, prepared by cryofixation and ultracryomicrotomy. Comparisons with measurements on isolated granules indicate considerable differences in alkali metal ion concentrations between the two methods of analysis, whereas calcium and phosphate concentrations were comparable. EELS was used to determine water content in fast-frozen sections and thereby to estimate the granular membrane potential. Elemental distributions also provided some indications of the ionic exchange mechanisms that are operative.

In collaboration with the Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases (NIAID), elemental distributions in *trypanosoma cruzi* were obtained from two clones. The collaboration revealed that the iron content of one clone was twice that found in the other, with most of the iron being found in mitrochondria. Analytical electron microscopy could prove to be useful in characterizing the cells. We are slowly converting the Group's computational facilities from use of an aging minicomputer to a distributed network of Macintosh II work stations. The minicomputer will be retired next year.

Microanalytic Methods Group

Research in the area of physical chemistry of biological macromolecules has involved collaborations with several Institutes within NIH. Extensive effort has been given to using IBM XT and Macintosh II computers as the basis of data acquisition systems for the analytical ultracentrifuge. New methods have been developed for rapidly obtaining sedimentation coefficients, diffusion coefficients, and molecular weights in a collaboration with NIDDK. Studies on the interactions of fibrinogen and fibrinogen D and E fragments with various plasma proteins involved in the clotting and fibrinolytic process have been continued in a collaboration with the National Institute of Dental Research (NIDR). Studies on the associative properties of synapsin and cell adhesion peptides from fibronectin have continued with NCI. Investigation of the activity coefficients of compounds used for density gradient ultracentrifugation is now in progress. Further progress has been made in the techniques of mathematical modeling used for the analysis of data obtained in these studies and has significantly enhanced the quality of the results obtained.

Applied Clinical Engineering Section

The Applied Clinical Engineering Section (ACES) provides a variety of biomedical engineering services to laboratories located in the NIH Clinical Center. Research projects are supported by expertise in design and development of biomedical instrumentation in a variety of areas, including blood pressure and flow measurement, microcalorimetry, thermal measurement, electro-optics, microelectronics, transducer design, automated data collection and analysis, and hardware and software design for microcomputer-based systems.

ACES continues to collaborate with the Laboratory of Chemical Biology, NIDDK, on development of noninvasive monitoring techniques for sickle cell disease. These studies include determining the accuracy of pulse oximeters for monitoring oxygen saturation in sickle cell blood, and monitoring the effects of new treatments on microvascular blood flow. *In vitro* systems for monitoring red blood cell parameters, such as transit time and deformability, were also developed this past year.

A computer-based system to calibrate noninvasive blood pressure monitors was developed for the Clinical Center. The system simulates the events in the blood pressure measurement cycle, as detected by oscillation-type blood pressure monitors, enabling the calibration of such devices.

Methods are being developed for the noninvasive determination of tooth vitality based on the optical measurement of oxygen saturation of blood in tooth pulp. Mathematical and physical models of light scattering and absorption in tissue are being constructed to elucidate the theoretical basis of pulse oximetry. Results of these studies will assist in the development of novel types of oximeters.

As mentioned in the opening paragraphs of this report research continues in the design of faster and more sensitive microcalorimeters.

Collaboration with the Surgery Branch, NHLBI, continues in a study of left-ventricular mechanics and the effects of mitral value replacements. In addition, the development of a system for hemodynamic evaluation of mechanical and bio-prosthetic heart values continues.

In collaboration with the Laboratory of Cell Biology and Genetics of NIDDK, a system was designed to study the characteristics of ionic channels present on the plasma membrane of bovine chromaffin cells. The effects of inhibitory drugs and various membrane potentials were measured by monitoring event duration and amplitude. Distribution statistics were determined from the histograms of the collected data.

The Medical Neurology Branch of NINCDS collaborated with ACES in the design of a system to obtain real-time measurements of electroencephalographic (EEG) spikes. The system is used to screen anticonvulsant drugs that block the effects of chemoconvulsants.

An instrument to display the amount of decaying radionuclide tracer administered to each patient during diagnostic nuclear medical procedures was designed for the Department of Nuclear Medicine, Clinical Center. The design included the conversion of a single-user monitoring system to a multi-user system that simultaneously monitors three patients at separate imaging area locations.

A cooling system for use in a study of the effect of lowered brain temperatures on depressed patients was designed and fabricated for the Clinical Psychobiology Branch, National Institute of Mental Health (NIMH).

Conditions of the power lines in the Clinical Center are under investigation to determine whether they are the cause of electrical noise problems in ongoing electro-oculography studies in the Clinical Branch of the National Eye Institute (NEI).

ACES continued to participate in clinical engineering activities within the hospital portion of the Clinical Center. All incidents in which patients or personnel were injured by electricity were investigated. Other aspects of electrical safety and equipment standards were reviewed and monitored through representation at meetings of the Clinical Center Safety and Standardization Committees.

Chemical Engineering Section

The Chemical Engineering Section provides support to the NIH in pharmacokinetics, transport phenomena, fluid mechanics, biomaterials, and instrumentation. Major collaborative research and development projects typically involve one or more engineering staff and researchers from the biomedical sciences in a close interaction with the objection of advancing our understanding of biological processes and improving clinical practice.

Modeling of biochemical pathways has focused on elucidation of reactions of the anti-cancer drug cisplatin (DDP) *in vitro* and a general model of the folate cycle in the MCF-7 human breast cancer cell line. The hydrolysis products of DDP in buffered chloride solutions have been measured for 25 hours by HPLC/electrochemical detection techniques over a pH range of 5.5 to 7.8. A kinetic model has been developed that accurately accounts for the concentration-time profiles of both parent drug and monoaquo/monohydroxo derivatives. Furthermore, the rate constant describing the reverse monoaquo-to-parent DDP reaction has been determined, as well as the acid dissociation constant of the monoaquo/monohydroxo species. Extrapolations from this model to the pH and chloride levels found in plasma ultrafiltrate reveal that, while the relatively alkaline pH of plasma (7.4) accounts for a moderate fraction of the observed drug reactivity, pH alone does not account for all reactivity.

The folate cycle model has been completed for the MCF-7 breast cancer cell line. It consists of 21 ordinary differential equations describing the principal reactions of the folate cycle, as well as those describing the glutamation, deglutamation, and transport of methotrexate (MTX). The folate cycle model has been examined for its sensitivity to inclusion of enzyme activities that are cell cycle dependent.

Principles of chemical reaction engineering have been applied to the development of pharmacokinetic models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and humans. They provide a plausible set of equations that can be used to extrapolate data from animals to humans and thereby improve chemotherapy and risk assessment.

Consideration of regional drug delivery has continued with emphasis on intra-arterial and intracavitary administration. Drug streaming from arterial catheters appears to be a frequent problem leading to nonuniform distribution of drug in the infused tissue and compromising studies of toxicity and therapeutic effect. Work is in progress on the development of a physiological pharmacokinetic model for methyl mercury and inorganic mercury in the rat. Work is also in progress on the adaptation of a pharmacokinetic model for cis-diamminedichloroplatinum(ii) to other platinum containing complexes. Increased emphasis has been placed on the pharmacokinetics of macromolecules, such as monoclonal antibodies and immunotoxins.

Transport theory has been applied to the analysis of data from vitreous fluorophotometry and to understand better the characteristics of a microdialysis probe.

Vitreous fluorophotometry (VFP) is a clinical procedure for measuring the spatial distribution of fluorescence along the optical axis in a human subject's vitreous, following administration of a fluorescent dye. One disease for which VFP may be useful is diabetes and its associated pathology, diabetic retinopathy. Additional goals for this project are to evaluate VFP for use in (1) screening for early detection, and (2) monitoring for treatment efficiency in diabetes and other pathological conditions. Analysis of measurements on a population of 22 normal volunteers, including six who were measured again on a different day, led to several findings. All of the existing analysis protocols have deficiencies that are generally overcome by the analysis scheme developed in the Chemical Engineering Section. The permeability value that we obtain as a measure of the blood-retinal barrier leakiness has a smaller variance for the normal population than the measures used by other analysis schemes. However, none of the leakiness measures consistently indicates a statistically significant difference between normals and an early diabetic population of 12 patients with minimal retinopathy and 12 patients with no retinopathy.

Microdialysis probe technology provides a means for sampling diffusible extracellular constituents in tissue. However, the relationship of the probe effluent concentrations to their tissue counterparts is a complex function of solute molecular weight, solute physicochemical properties, tissue properties, probe membrane properties, probe geometry and perfusion rate, and the trauma of probe insertion into the tissue. These dependencies will be studied in order to improve the quantitative usefulness of the technology. The focus of applications is the brain in connection with Parkinson's disease and transplant therapy. Solutes of particular interest are dopamine and its metabolites. A mathematical model has been developed for the transient and steady-state operation of a continuously-perfused probe that samples solute supplied to the tissue at a constant concentration and undergoing first order reaction in the tissue.

The Section's work in experimental fluid mechanics has emphasized model systems for the evaluation of catheters and infusion techniques. Flow models are useful tools for studying hemodynamic events relating to use of catheters. Such models can reduce the need for animal experimentation and allow the investigator the opportunity to conduct experiments under controlled laboratory conditions. Streaming of dye shown to occur in a transparent model of the internal carotid artery and its major branches has been validated consistently in experimental animals and in clinical studies. The simultaneous infusion of incompatible drugs, such as Dilantin and TPN solution, through multilumen catheters has the potential for adverse interaction of drugs, such as precipitation of Dilantin at the catheter tip. The precipitation of Dilantin has been recorded on videotape, when Dilantin and TPN are infused simultaneously through a Hickman double-lumen catheter into a transparent model at rates of 1.6 ml/min. Preliminary assays indicated that the amount of precipitate varies depending on catheter position, flow rate, and infusion rate.

Electrical and Electronic Engineering Section

The objective of the Electrical and Electronic Engineering Section is to bring the power of modern electronic technology to bear on the needs of biomedical research. Special expertise in areas such as electro-optics, microprocessors, video, and general electronic circuitry has provided support for a wide variety of intramural research projects.

The focus of our electro-optic efforts is the identification and development of new applications for lasers in biomedical research, diagnosis, and therapy. This has involved evaluation of numerous laser/fiber-optic systems and development of a general theory for the interaction of light with physiological materials. An instrument using laser Doppler technology to quantify peripheral blood circulation parameters has been developed, and the features of this device have now been incorporated into several commercial instruments.

Our program with NHLBI in laser angioplasty has broadened understanding of this therapeutic modality. We have demonstrated selective ablation using argon and flash-lamp pumped dye lasers and characterized their clinical limitations, showed the inherent limitations of excimer laser systems and further developed new technology using pulsed Er:YAG laser and zirconium fluoride optical fibers. A careful clinical evaluation of the optical technique of fluorescence analysis via fiberoptic catheters as a means for sensing atherosclerotic plaque has led to clinical trials of laser angioplasty in patients with totally-occluded peripheral (leg) or coronary arteries. The potential for accidental perforation of the arterial wall is still a serious one. Efforts are under way to achieve an adequate ability to direct the laser beam by delivering its energy at a slight angle to the axis of the catheter and rotating the catheter appropriately.

Our collaboration with Radiation Oncology Branch and the Surgery Branch, National Cancer Institute (NCI), on the development of techniques for photochemical treatment of cancer has moved rapidly into human trials. This method involves direct illumination of tumors with laser light after the patient has received a photochemical (hematoporphoryin derivative) with specific activity against malignant tissue. The local photochemical generation of singlet oxygen kills the tumor cells, providing a focal therapy with minimal effects on normal tissue. In the past year we have improved dosimetry and light delivery techniques for certain skin, lung, and bladder cancers. We are also examining new photochemicals and other ways to extend this form of therapy. We have, for example, just completed a computerized system for monitoring light dosage during surgery. The system uses signals from 8 calibrated photo-diodes that are sensed on a moment-to-moment basis.

We have applied our experience in laser photochemistry to studying means of photochemical destruction of viral and bacterial contamination of blood and blood products. One goal of this collaboration with the Center for Biologics Evaluation and Research, FDA, is to develop a non-invasive photochemical treatment of blood stored in transfusion bags to reduce the risk of transmitting AIDS and other infectious diseases. We have evaluated single and multiple-photon excitation of DNA and proteins for the dose response of human blood cells and viruses. An efficacious range of laser light doses has been determined that destroys virus, but does no significant damage to serum and platelet concentrates. Currently we are evaluating the potential of increasing therapeutic efficiency by the introduction into the blood of selective photochemicals. The effects on the blood components and infectious agents of light and photochemical agents, alone and in combination, are critical components of this investigation.

We have begun new electro-optic projects in the areas of pico-second fluorometry and high speed spectrophotometry. One instrument under development can read absorptions at 100 wavelengths simultaneously one-hundred thousand times per second.

We are continuing to support the Electronic Patient Monitoring and Identification System for the 12E nursing unit of the National Institute on Aging (NIA). Work was performed to improve the frequency stability and battery life of the patient-worn transmitters, eliminating the need for periodic adjustments to the modulating frequency of the transmitters. The experience gained in the development and operation of the system is now being applied to the broader needs of memory-impaired older persons through the support of an interagency group that includes the National Institute on Aging, Veterans Administration, National Aeronautical and Space Administration, Administration on Aging, and National Institute of Handicapped Research. In addition, similar technology is being used to design a noninvasive temperature monitoring system for infants with hypohydrotic ectodermal dysplasia, a hereditary condition in which there is failure of development of sweat glands, hair, and teeth. Because these infants cannot cool their bodies, death can result from any illness associated with fever. The infants in the study will wear a miniature radio transmitter that broadcasts the body temperature. A radio receiver processor unit will monitor the transmitted signal and sound an alarm when the infant's temperature rises above a safe value.

The support of the NIH Bio Technology Unit (Pilot Plant) continues by providing additional means of data acquisition, process control, and data analysis for production and research. Two new tissue culture fermentors have been acquired, and we are developing computer-based data acquisition systems for them. A second 5-10 liter research system is being produced, similar to the system now in use. All of the control and analysis programs continue to be upgraded to provide better results and efficiency. The Section is continuing to improve the computer-based eye tracking system built for the NIMH. The protocol is being expanded to include the testing of the eye tracking function of family members of schizophrenics, and a portable system is being planned to allow testing at home. Other laboratories at the NIH have become interested in this line of research and have requested systems of their own.

The magneto-encephalography program in collaboration with NINCDS and Division of Computer Research and Technology (DCRT) has focused on the so-called "inverse modelling problem," correlation of MEG and EEG data, and computerized classification of epileptic discharges. Introduction of current dipoles of various locations and orientations into a model permitted experimental assessment of the effects of return currents, when the geometry was too complex for theoretical analysis. The principal long-range goal continues to be the spatial localization of epileptic foci in three dimensions. In the related area of magnetic neural stimulation, we are using circuit-analysis software to optimize parameters for magnetic stimulation, as well as to develop methods for computer simulation of the electric field patterns induced by various coil configurations.

We are continuing to support the Neuro-PET scanner and are developing a proposal to use it in a study of general methods to achieve higher resolution in PET scanning. Analysis of the complex interactions among various parameters indicates that the comparatively small ring diameter of the Neuro PET may be essential for achieving high resolution, good signal-to-noise ratio, and reasonable scan times, but the device may also require more sophisticated corrections for scatter, dead time, random coincidences, and attenuation.

Mechanical Engineering Section

The Mechanical Engineering Section conducted a diversity of collaborations with scientists involving analytical and experimental studies and the development of specialized instrumentation. The year saw the publication of a compilation of proceedings from two NIH-INSERM workshops on Cardiovascular Dynamics and Models held in Bethesda in 1985 and in Paris in 1987. This monograph summarizes collaborative research in myocardial blood flow, ventricular mechanics and energetics, ultrasonic methods, and wave propagation and arterial dynamics. One project, in collaboration with the Cardiology Branch of NHLBI, involved improvements in detecting the time course of myocardial boundaries in M-mode echocardiograms. Another project, with the Surgery Branch of NHLBI, is validating a theoretical model of left ventricular performance, using ultrasonic crystals to measure of ventricular dimensions. Once validated, the model will be used to assess means for long-term preservation of hearts for transplantation. In a project with the Laboratory of Cardiac Energetics of NHLBI, we will test a theoretical model of myocardial energetics, using NMR imaging of ventricular volume.

The MES continues theoretical and experimental studies of hyperthermia as an adjunctive treatment for cancer. Methods employed include measurement of spatial and temporal variation in the temperature field of tissues subjected to radio-frequency electromagnetic radiation. Thermal model computations have shown that blood flow thermoregulation in muscle tends to dominate the resulting thermal pattern, limiting the temperature of the heated normal tissue to a temperature of 41-42°C. The thermal dose to a non-thermoregulated tumor is very high, and the dose to the normal, profused surrounding tissue is relatively small if the radiofrequency (rf) energy is focused primarily in the tumor. This is accomplished by phase shifting the dipoles of the applicator or by increasing the amplitude of the rf-energy emitted from the two dipole pairs located closest to the tumor. In order to increase the safety and effectiveness of applying these treatments to limbs, we are developing a new noninvasive method for measuring temperature using magnetic resonance imaging. This method of measuring has a resolution of better than 0.5°C, in plastic phantoms containing gels with electric properties resembling tissue, as confirmed by measurements using fiber-optic probes.

A new project is the study of the electromechanochemistry of polyelectrolyte hydrogels and, in particular, their remarkable swelling behavior. The physical and chemical properties of these gels are being exploited in the design of devices that sense touch and perform mechanical work. Physical chemistry and statistical and continuum mechanics provide the underpinnings of mathematical models that are being developed to describe their equilibrium and dynamic behavior, while experiments are being performed to determine their physical and chemical properties.

A high-speed, no-moving-parts, reflected-light laser scanning confocal microscope is under development. The NEI will use the device, initially, for corneal research, making use of the ability of confocal microscopes to focus on a single layer of tissue. Major components of the system have been built and overall system integration and testing are in progress.

Final testing is virtually complete on a computer-controlled instrument that scans tissue culture dishes and locates cell colonies that have been fluorescently labeled so that they can be isolated and cloned. An X-Y recorder mechanism moves the dish in a raster pattern beneath a focused laser beam. After specialized electronic circuitry eliminates most artifacts, the device scribes an "x" on the bottoms of dishes at the locations of colonies. The instrument will be used for cells that cannot be put through a cell sorter.

Work continues on the system for three-dimensional histological reconstruction involving a remotely-controlled miniature microtome, located inside a scanning electron microscope. A microcomputer-based instrument for delivering precisely one cell into each well of a titre tray is near completion. The instrument, based on a Coulter-counter technique, should significantly improve efficiency of cell cloning.

A new project has been initiated to develop an automated device to study the *in vitro* morphological response of sickle-cell erythrocytes to changes in the partial pressure of oxygen. Red blood cells will be fixed in a flow cell mounted on a microscope while a videocamera transmits the image to a computer. Pattern recognition algorithms will determine which of the cells in the field has sickled. The pO_2 vs time curve is an important factor in sickling, so the flow system has been designed to allow the oxygen saturation to be changed very quickly and reproducibly (such as from arterial to venous levels). The automated device will eliminate the manual cell counting traditionally required in this area of research, thus helping researchers to monitor patients and develop new therapeutic agents.

Scientific Equipment Services

Scientific Equipment Services (SES) is continuing to provide the NIH scientific community with equipment design, fabrication, repair and rental services. During the past few years, SES has striven to increase the number of instrumentation-related services it offers to the NIH scientific community, improve efficiency, reduce the time researchers spend in non-research activities (such as equipment procurement and equipment repair), and reduce the cost of services provided. Specific activities are:

1. Sale of New Scientific Equipment: Effective mid-FY 89, SES will begin to sell commonly-used laboratory instruments, such as pH meters, waterbaths and spectrophotometers. BEIB will stock these instruments and researchers will be able to obtain them within one day, instead of going through the normal NIH procurement process. Aside from the convenience to the researcher, we anticipate dollar savings to the NIH through reductions in the number of purchase orders processed by procurement and decreased delays to research projects.
2. Sale of Equipment from Scientific Equipment Rental Program (SERP) Inventory: In response to requests from the Institutes, researchers who rent equipment from SERP for more than six months will be permitted to purchase the equipment. (In order to prevent the possibility of a rapid depletion of SERP equipment, however, sales will be limited to 25% of the value of equipment that the Institute rented on the last day of the prior fiscal year.)
3. Equipment Management Program for Patient Care Equipment: SES is in the process of developing a comprehensive program for the management of patient care equipment in the Clinical Center. The program includes: equipment evaluations, incoming/new equipment

inspections, electrical safety testing, performance testing, and an on-line system that reports on equipment inventories and repair histories. This plan is intended to reduce maintenance and repair costs and provide the Clinical Center with up-to-date information on its equipment.

4. Management of Equipment in Central Shared Animal Facilities: SES is exploring the feasibility of developing and managing a program for the sharing of equipment in NIH's proposed Central Shared Animal Facilities. Such a program would reduce operating costs and the time required to obtain new equipment through sharing of equipment among the Institutes.
5. Reduction of Full-Service-Contract Equipment Maintenance: SES is exploring the concept of reducing the cost of commercial, full-service contracts purchased by NIH researchers. This includes a systematic review of existing contracts to identify areas where we can provide the service at lower cost.

SES has developed a computerized job control system that will assure that all work is performed in a timely manner by allowing managers to review the status of work assigned to technicians. In addition, internal procedures have been modified to expedite ordering of components.

Publications

Andrews SB, Leapman RD, Landis DMD, Reese TS. Activity-dependent accumulation of calcium in Purkinje cell spine organelles. Proc Nat Acad Sci USA 1988;85:1682-5.

Barth KH, Lutz RJ, Kremers PW, Miller DL. Improved mixing of low flow hepatic artery infusion with small caliber double lumen balloon catheter. Invest Rad 1988:519-23.

Blumentals II, Skaja AK, Kelly RM, Clem TR, Shiloach J. Effect of culturing conditions on the production of exotoxin A by pseudomonas aeruginosa. Ann NYAC 1987;506:663-8.

Bolten JG, Morrison PF, Resetar SA, Wolf KA. Health risk from a coal tar disposal site (R-3595-EPRI). Santa Monica, CA: Rand, 1988;96.

Bonner RF, Prevosti MB, Leon MB, Levin K, Tran D. New source for laser angioplasty: Er:YAG laser pulses transmitted through zirconium fluoride optical fiber catheters. In: Katzir A, ed. Optical fibers in medicine III. Bellingham, WA: Society of Photo-Optical Engineers, 1988;288-93.

Bonner RF, Smith PD, Prevosti LG, Bartorelli A, Almagor Y, Leon MB. Laser sources for angioplasty. In: Abella GS, ed. Lasers in cardiovascular medicine and surgery. Boston: Martinus Nijhoff (in press).

Bonner RF, Smith PD, Prevosti LG, Leon MB. New sources for laser angioplasty, Er:YAG, excimer lasers, and non-laser hot-tip catheters. In: Interventional cardiology: future directions. Baltimore; Mosby (in press).

Boretos JW. Alumina for bioceramics. In: Hart LD, ed. Handbook of science and technology on alumina chemicals. American Ceramics Society (in press).

Brun P, Chadwick RS, Levy BI (eds). Cardiovascular Dynamics and Models. Paris: Institut National de la Sante et de la Recherche Medicale, 1988 (Colloque INSERM; vol 183).

Chadwick RS. A theory for diastolic zero flow pressure in the beating heart. Automedica 1987;9:91.

Chadwick RS, Brun P. A theoretical model of left ventricle filling and interpretation of ecographic and Doppler mitral wave forms. In: Brun P, Chadwick RS, Levy BI, eds. Cardiovascular dynamics and models. Paris: Institut National de la Sante et de la Recherche Medicale, 1988;339-48. (Colloque INSERM; vol 183).

Chadwick RS, Ohayon J. Axisymmetric geometrical effects in ventricular mechanics. In: Brun P, Chadwick RS, Levy BI, eds. Cardiovascular dynamics and models. Paris: Institut National de la Sante et de la Recherche Medicale, 1988;193-202. (Colloque INSERM; vol 183).

Chadwick RS, Ohayon S. Mechanics of the arteriole wall. In: Proc world congress on medical physics and bioengineering, August 6-12, San Antonio, Texas. 1988;349.

Chadwick RS, Ohayon J. Strain energy stored in the myocardium at end-systole as a filling index of heat. In: Proc Soc Eng Sci, Berkeley, California. 1988;96.

Chadwick RS, Ohayon J. A theory for local myocardial energetics and oxygen demand based on an active rheological law. In: Brun P, Chadwick RS, Levy BI, eds. Cardiovascular dynamics and models. Paris: Institut National de la Sante et de la Recherche Medicale, 1988;151-9. (Colloque INSERM; vol 183).

Chadwick RS, Tedgui A, Michel JB, Ohayon J, Levy B. A theoretical model for myocardial blood flow. In: Brun P, Chadwick RS, Levy BI, eds. Cardiovascular dynamics and models. Paris: Institut National de la Sante et de la Recherche Medicale, 1988;77-90. (Colloque INSERM; vol 183).

Chapman B, Turner R, Ordidge RJ, Doyle M, Cawley M, Coxon R, Glover P, Mansfield P. Real-time movie imaging from a single cardiac cycle. Magn Reson Med 1987;5:246-54.

Charny C, Guerquin-Kern J-L, Levin RL. Energy deposition patterns in amputated human lower legs heated with a mini-annular phased array. Med Phys 1988;15:17-23.

Charny CK, Levin RL. Bioheat transfer in a branching countercurrent network during hyperthermia. Trans ASME J Biomechan Eng 1988 (in press).

Charny CK, Levin RL. Heat transfer normal to paired arteries and veins embedded in perfused tissue during hyperthermia. Trans ASME, Biomechanl Eng 1988 (in press).

Charny C, Levin RL. Simulations of MAPA and APA heating using a whole body thermal model. IEEE Trans Biomed Eng 1988;BME-35:362-71.

Charny C, Levin RL. A whole body thermal model of man with a realistic circulatory system. IEEE Trans Biomed Eng 1987;BME34:375-84.

Charny CK, Levin RL. A whole body thermal model of man with a realistic circulatory system. In: Chato JC, Diller, TP, Diller KR, Roemer RD, eds. Heat transfer in bioengineering and medicine; vol BED-7. New York: American Society of Mechanical Engineers, 1987;45-50.

Chen C-N, Kan L-S. An iterative phase-correction program for nuclear magnetic resonance (NMR) spectra. Comput Methods Programs Biomed 1988;26:81-4.

Coldefy H, Levin RL. Theoretical results of power deposition in targets irradiated by the MAPA. IEEE Trans Biomed Eng 1988 (in press).

Dedrick RL. Arterial drug infusion: pharmacokinetic problems and pitfalls. JNCI 1988;80:84-9.

Dedrick RL. Pharmacokinetics. Proceedings of the Engineering Foundation Conference on Chemical Engineering Education in a Changing Environment, Santa Barbara, CA, January 17-22, 1988 (in press).

Dedrick RL, Flessner MF. Pharmacokinetic considerations on monoclonal antibodies. In: Proceedings of the 2nd conference on immunity to cancer, Williamsburg, VA, Nov 9-11, 1987 (in press).

DeRossi D, Lazzeri L, Domenici C, Nannini A, Basser P. Tactile sensing by an electromechanochemical skin analog. Sensors and Actuators (in press).

Dvorak JA, Engel JC, Leapman RD, Swyt CR, Pella PA. T. Cruzi: elemental compositional heterogeneity of cloned stocks. Mol Biochem Parasitol (in press).

Dvorak JA, Whelan WL, McDaniel JP, Gibson CC, Kyung Joo Kwon-Chung. Flow cytometric analysis of the DNA synthetic cycle of candida species. 1987;55:1490-97.

Eden M. Computer technology and biomedical instrumentation. In: Cutting edge technologies and microcomputer applications for developing countries. National Academy of Sciences. Report of an ad hoc panel on the use of microcomputers for developing countries. Boulder, CO: Westview Press, 1988;199-220. (Westview special studies in science, technology and public policy).

Eden M. Trends in biomedical instrumentation research. In: Technologie medicale de l'innovation au produit et a son utilization optimale. EPFL-Lausanne, Switzerland. A conference held on October 21-22, 1988. 7-12.

Farris FF, Dedrick RL, King FG. Cisplatin pharmacokinetics: applications of a physiological model. Toxicol Lett 1988;43:117-37.

Fiori CE. The new electron microscopy: imaging the chemistry of nature. Anal Chem 1988;60(Fundamental Reviews):86R-90R.

Fiori CE, Leapman RD, Swyt CR, Andrews SB. Quantitative x-ray mapping of biological cryosections. Ultramicroscopy 1988;24:237-50.

Foster MC, Hagins WA. Concentrations of ions measured as a function of position along frog retinal rod outer segments. Biophys J 1988;53:389a.

Guerquin-Kern J-L, Hagmann MJ, Levin RL. Experimental characterization of helical coils as a hyperthermia applicator. IEEE Trans Biomed Eng 1987;35:46-52.

Hagmann MJ, Levin RL. Procedures for noninvasive electromagnetic property and dosimetry measurements. IEEE Trans Microwave Theory Techniques (in press).

Hedges KL, Hoult DI. The techniques of rotating frame selective excitation and some experimental results. J Magn Res 1988;79:391-403.

Hommer D, Sunderland T, Clem T. Smooth pursuit and saccadic eye movements in patients with Alzheimer's dementia and schizophrenia. Soc Neurosci Abstr 1987;13,Part 1:171.

Hoult DI, Chen C N, Hedges LK. Spatial localization by rotating frame techniques. Ann NYAS 1987;508:366-75.

Howseman AM, Stehling MK, Chapman B, Coxon R, Turner R, Ordidge RJ, Cawley MG, Glover P, Mansfield P, Coupland RE. Improvements in snapshot nuclear magnetic resonance imaging. Brit J Radiol 1988;61:822-8.

Johnson JE, Jr., Friend D, Leapman R, Peters K, Kanaya K, Baba N, Naka M, Salpeter M, Nesland J, Johannessen JV, Porter K. New perspectives of electron microscopy in medicine. In: Russo J, Sommers SC, eds. Tumor dignosis by electron microscopy, vol 2. Philadelphia: Medical Publishers 1988;1-66.

Lawrence W, Norton J, Harvey A, Gorschboth C, Talbot T, Brotendorst G. Wound healing in sarcoma bearing rats: tumor effects on cutaneous and deep wounds. J Surg Oncol 1987;35:7-12.

Leapman RD. Application of parallel recorded EELS to analysis of beam-sensitive compounds. In: Baily GW, ed. Proceedings of the 46th annual meeting of the Electron Microscopy Society of America. San Francisco: San Francisco Press 1988;632-3.

Leapman RD, Ornberg RL. Quantitative electron energy loss spectroscopy in biology. Ultramicroscopy 1988;24;251-68.

Leapman RD, Swyt CR. Unravelling of overlapping core edges by multiple least squares fitting. Ultramicroscopy (in press).

Leon MB, Lu DY, Prevosti, LG, Macy WW., Smith PD, Granovsky M, Bonner RF, Balaban RS. Human arterial surface fluorescence: atherosclerotic plaque identification and effects of laser atheroma ablation. J Am Coll Cardiol 1988;12:94-102.

Levy B, Samuel J, Chadwick RS. Morphological analysis of myocardial microvasculature in the rat during diastole and systole. In: Brun P, Chadwick RS, Levy BI, eds. Cardiovascular dynamics and models. Paris: Institut National de la Sante et de la Recherche Medicale, 1988;65-71. (Colloque INSERM; vol 183).

Lutz RJ. Physical models of hemodynamic systems. Abstract for Ninth Annual IEEE Conference on Engineering in Medicine and Biology. Boston, MA, November 13, 1987.

Lutz RJ, Dedrick RL. Implications of pharmacokinetic modeling in risk assessment analysis. Environ Health Perspect 1987;76:97-106.

Lutz, RJ, Miller DL. Mixing studies during hapatic artery infusion therapy in an in vitro model. Cancer 1988;62:1066-73.

Manyak MJ, Matthews DM, Smith PD, Nochomovitz LE, Glatstein E, Russo A. Response of normal canine ureter to photodynamic therapy using a cylindrical fiber. Urology 1988;139:199-203.

Manyak MJ, Russo A, Smith PD, Glatstein E. Photodynamic therapy. J Clin Oncol 1988;6:380-91.

Manyak MJ, Smith PD, Harrington FS, Steinberg S, Glatstein E, Russo A. Protection against dihematoporphyrin ether photosensitivity. Photochem Photobiol 1988;47:823-30.

Morrison PF. Effects of time-variant exposure on toxic substance response. Environ Health Perspect 1987;76:133-40.

Mavrovouniotis GM, Brenner H, Bungay PM. Hindered sedimentation, diffusion, and dispersion coefficients for Brownian spheres in circular cylindrical pores. J Colloid Interface Sci 1988;124:269-83.

Mudd CP, Berger RL. A computer-controlled all tantalum stopped-flow microcalorimeter with microjoule resolution. J Biochem Biophys Methods (in press).

Mudd CP, Berger RL, Carducci JS. The kinetics and enthalpy of the NAD-NADase reaction as measured by stopped flow microcalorimetry. Proceedings of the IV Polish conference on calorimeters and thermal analysis, Pkkiat, Poland, 1988.

Mudd CP, Berger RL, Remeta DP, Breslauer KJ. Decomposition of microcalorimeter thermograms in the 100 microjoule range. Biophys 1988;53:480a.

Mudd CP, Remeta DP, Berger RL, Breslauer KJ. Application of stopped flow microcalorimetry for the determination of daunomycin-deoxypolynucleotide binding enthalpies. Biophys J 1988;53:480a.

O'Callaghan C, Small P, Chapman B, Coxon R, Glover P, Turner R, Jaroszkiewicz G, Howseman AM, Mansfield P, Coupland RE, Milner AD, Milner M. Determination of individual and total lung volume using nuclear magnetic resonance echo-planar imaging. Ann Radiol 1987;30:470-2.

Ohayon J, Chadwick RS. Effects of collagen microstructure on the mechanics of the left ventricle. Biophys J (in press).

Ohayon J, Chadwick RS. Theoretical analysis of the effects of a radial activation wave and twisting motion on the mechanics of the left ventricle. Biorheology 1987;25:435-47.

Ohayon J, Chadwick RS, Lewkowicz M. Fluid-fiber-collagen description of the myocarduim applied to different left ventricular geometrics. In: Proceedings of the world congress on medical physics and biomedical engineering, August 6-12, 1988, San Antonio, Texas. 179.

Ordidge RJ, Coxon R, Howseman AM, Chapman B, Turner R, Stehling MK, Mansfield P. Snapshot head imaging at 0.5T using the echo-planar technique. Magn Reson Med 1988;8:110-5.

Ornberg RL, Kuijpers GAJ, Leapman RD. Electron probe microanalysis of the subcellular compartments of bovine adrenal chromaffin cells: comparison of chromaffin granules in situ and in vitro. J Biol Chem 1988;263:1488-93.

Peterson JI. Optical Sensors. In: Webster JG, ed. Encyclopedia of medical devices and instrumentation; vol 3. New York: John Wiley and Sons, 1988;2121-34.

Prodouz KN, Fratantoni JC, Boone J, Bonner RF. Use of Laser-UV for inactivation of virus in blood products. Blood 1987;589-92.

Roy MS, Podgor MJ, Grunberger G, Carl J, Bungay PM, Ellis D. Fluorophotometrie dans le diabete insulino-dependant avec retinopathie minime ou absente. Ophthalmologie 1987;2:151-4.

Saris SC, Shook DR, Blasberg RG, Dedrick RL, Doppman JL, Bankiewicz KS, Blacklock JB, Oldfield EH. Intracarotid drug delivery with diastole-phased, pulsed infusion. J Neurosurg 1987;67:721-5.

Small JA, Newbury DE, Mykzebust RL, Fiori CE. An electron/x-ray optical bench for the measurement of fundamental parameters. In: Newbury DE, ed. Microbeam analysis 1988. San Francisco: San Francisco Press;263-70.

Stehling MK, Howseman AM, Chapman B, Coxon R, Glover P, Turner R, Ordidge RJ, Jaroszkiewicz G, Mansfield P, Morris GK, Dutka D, Worthington BS, Coupland RE. Real-time NMR imaging of the heart: observation of coronary vessels. Lancet 1987;ii:964-5.

Steven AC, Trus BL, Maizel JV, Unser M, Parry DAD, Wall JS, Hainfeld JF, Studier FW. The molecular structure of a viral receptor-recognition protein - the GP17 tail-fiber of bacteriophage T7. Mol Biol 200 1988;351-65.

Turner R. Minimum inductance coils. J Phys E: Sci Instrum 1988;21:948-52.

Turner R. Perfusion studies and fast imaging. In: Rescigno A, Boicelli A, eds. Cerebral blood flow. New York: Plenum Publishing, 1988;245-58.

Unser M. Comments on 'A new approach to recursive Fourier transform' (Moeness G. Amin). Proceedings of the IEEE (in press).

Unser M, Eden M. Maximum likelihood estimation of linear signal parameters for Poisson processes. IEEE Trans Acoust Speech Signal Process 1988;36:942-5.

Unser M, Eden M. Multi-resolution feature extraction and selection for texture segmentation. IEEE Trans Pattern Anal Machine Intell (in press).

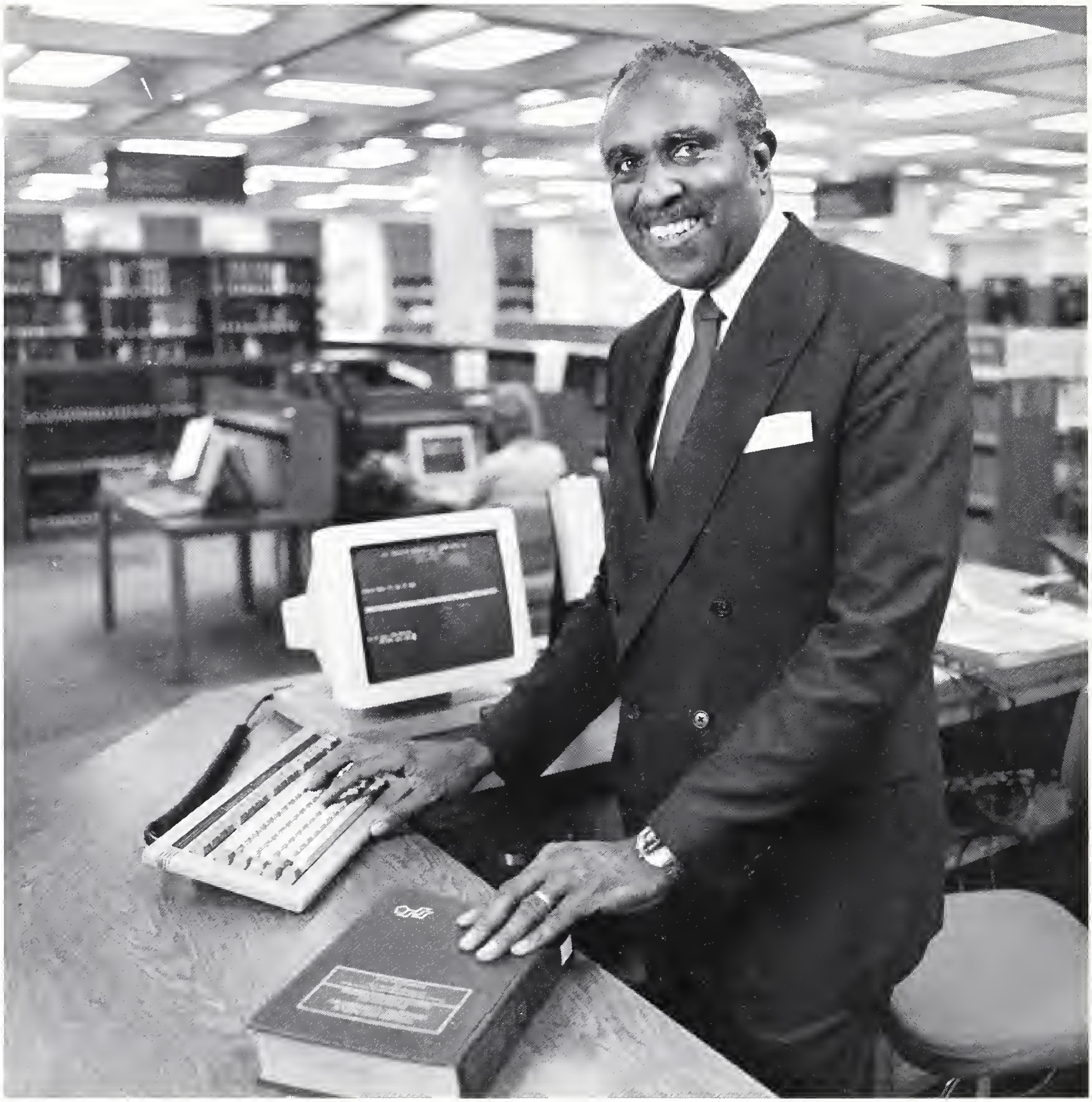
Unser M, Ellis JR, Pun, T, Eden M. Optimal background estimation in EELS. J Microsc 1987;145:245-56.

Unser M, Pelle G., Brun P, Eden M. Computer analysis of M-mode echocardiograms: estimation of spatial deformation with time. In: Brun P, Chadwick R, Levy B, eds. Cardiovascular dynamics and models. Paris: Institut National de la Sante et de la Recherche Medicale, 1988;304-10.

Unser M, Pelle G, Brun P, Eden M: Computer analysis of M-mode echocardiograms: sequential extraction of myocardial borders. In: Brun P, Chadwick R, Levy B, eds. Cardiovascular dynamics and models. Paris: Institut National de la Sante et de la Recherche Medicale, 1988;297-303.

Unser M, Trus BL, Eden M. Iterative restoration of noisy elastically distorted quasi-periodic images. Signal Process (in press).

Unser M, Trus BL, Steven AC, Eden M. Iterative restoration of high resolution micrographs of quasi-periodic structures. In: Goodhew PJ, Dickinson HG, eds. Proceedings of the 9th European congress on electron microscopy. vol 1. 211-2.



Willie Paige has worked in just about every component of the NIH Library except the Translation Unit during his 32 years of service there. He has been assisting the Library's users directly at the circulation desk for the past 22 years.

Library Branch

Carolyn Brown, Chief

The Library's involvement with a productivity review continued throughout the year. Conducted by a firm of recognized experts in the evaluation of information services, the review devised a new and detailed system of measurement of each area following the analysis of internal operations made last year.

Strategic planning meetings gave the opportunity for a complete overhaul of goals and objectives for the Library. All supervisory staff participated in a series of meetings to evaluate existing goals and plans, to remove those agreed by all to have been met, and to replace them with others. During the course of the year several improvements in service made revisions necessary because goals had to be set higher.

The review produced recommendations in several areas as well as an evaluation of current operations. The contracting of photocopy and shelving activities was a primary recommendation. Implementation of this recommendation was more than half accomplished as the year ended. Upon the retirement of two employees in shelving, this entire function was placed under contract, as was a large portion of the photocopying. Both activities are operating satisfactorily in spite of a substantial increase in workload.

Suggestions were also made associating the maintenance of the journal collection to subscriptions held by NIH laboratories and individuals. Under the assumption that journals subscribed to in laboratories and by individuals will be discarded after two years and the older volumes sought in the Library, the reviewers recommended that a journal for which there are at least four subscriptions somewhere at NIH should also be in the Library's collection.

Another recommendation was that space be allocated to the Library to provide a badly-needed periodicals reading room. The crowded upper level of the Library has very little space that is quiet enough to allow browsing the current literature. Space for storage of less-used items is also recommended, so that room is freed on the shelves for new acquisitions. This recommendation was already slated for fulfillment last year, with the promise of a room on Executive Boulevard.

Also mentioned was the burden imposed on the Library by heavy use from non-NIH individuals and organizations. Such usage increased noticeably after the metro opened. While recognizing the problems caused the Library by the presence of numbers of people who remove materials from the shelves and create lines at photocopy machines, the review concludes that societal benefits outweight the costs to the Library. Therefore the open-door policy is endorsed, but it is noted that effects should be monitored and reported each year.

Among other recommendations are an increased public relations effort, continued support for cooperative arrangements for local office collections, use of a local area network when one is available, and centralized acquisitions in the Library for all information-related materials at NIH.

An evaluation of the Library's services was conducted using surveys directed to Library users, observations and studies of staff activities and functions, and comparisons with other libraries. The NIH Library was judged to be quite economical at a cost of $400 a year per professional served. Budgets of most special libraries show costs of $500 to $1,500 per professional. A rough estimate of the alternative costs of acquiring the same information elsewhere is $1,700; the benefits of the services are estimated at $9,600 per professional. Performance of services is generally rated higher by users than performance-rating norms for 26 other exemplary libraries observed by the reviewers.

Automation

The decision had been made in the previous year to change the system supplier for the Library's online catalog. One purpose of the conversion was to provide a more up-to-date and responsive catalog; another was to combine catalog, circulation system, serials control, and acquisitions, previously operated with three different computer systems, into one. At the beginning of the fiscal year, in November, the first module, acquisitions, was implemented. Gradually over the year records were transferred from the old system to the new or were entered in the various modules. Approximately 15,000 journal order records and check-in cards were manually created for all serial titles for the serial control system. At the end of the year the complete new system was running in tandem with the old, and only a few adjustments remained before the old could be turned off completely. As this is accomplished, approximately $50,000 a year in costs for redundant systems will be saved, as well as a considerable number of employee hours hitherto devoted to duplicate entry of data.

Journal Review

The NIH Library, like many others dependent on scientific journals for current information, has been startled over the past few years at the price increases of subscriptions. This year was a particularly shocking one, with a cost rise so great that only a grant of extra funds saved the Library's budget. For the past four years a journal review by subject has been conducted, with the assistance of scientists advising in the area of their specialty. For the first time this year records of photocopy use, collected by the automated system as each volume was taken into the self-service area to be copied, were available to consult as a factor in making decisions about cancelling subscriptions. With the agreement of the Library Advisory Committee, a list was compiled of all journals costing $450 or more for a year's subscription; any of these that had been photocopied no more than once during 1986-1987 was cancelled. In further reviews, all subscriptions were monitored for photocopy usage and the lists advertised to allow comment or objections. The final cancellation lists for the year was of 207 titles, at a saving of $56,000. Although new journals appear yearly and some are added to the subscription list, the reviews continue and journals that are not read will not long be maintained.

Executive Boulevard Storage Area

The extra storage space given to the Library a year ago has finally materialized in September 1988 in a finished room at the Executive Plaza south building. A list of titles or parts of titles selected for infrequency of use has been compiled; these journals will be moved to Executive Boulevard, freeing space for easier reshelving and for newly-acquired volumes. Plans are made to use this Executive Boulevard space also as an information center for NIH staff located there. A small collection of journals will be provided, as well as copy service, retrieval by messenger of books or photocopies from the NIH Library, and reception of search requests.

Service Improvements

In fiscal year 1987 notices in the DRS Research Services Update stated that Library staff would demonstrate software designed to edit bibliographies and would act as consultants in automating reprint collections. At the same time demonstrations to teach GRATEFUL MED and MEDLINE for users wishing to do their own searching were announced in the NIH Calendar of Events. These programs were so successful that a 50 percent increase in demand was noted in FY 88.

Staff members are experimenting with other microcomputer software that may be helpful to NIH Library users. One of the Staff demonstrated bibliographic file maintenance software at the NIH Research Day, and will teach a short course on one microcomputer package.

To assist scientists in searching, the Library has installed a microcomputer with two versions of GRATEFUL MED in the reading room. An experimental version of GRATEFUL MED is offered for staff without cost and is monitored by the system supplier to observe their habits.

Though the number of classes teaching scientists to perform their own searches has doubled, the number of searches performed by the staff increased 11 percent over the year.

In FY 88, the Library saw an increase of four percent in the number of people using the Library and an equivalent increase in the number of items loaned to NIH staff. There was also a small increase in the number of reference requests.

Loan and photocopy requests processed by the interlibrary loan unit increased 10 percent in fiscal year 1988 over fiscal year 1987. Self-service photocopying increased 22 percent.

The reshelving of books and journals is now accomplished within an average of two to three working hours, a considerable improvement over past practice.

The translation unit added personal computers during the year and used the technology of desktop publishing to improve the format of NIH Library translations.

Staff training efforts have increased in the Reference and Bibliographic Services Section. Search service librarians with degrees in microbiology, nursing, chemistry, child development and statistics are giving a series of seminars for their colleagues to help improve search quality in all areas.

Services of the NIH Library

The NIH Library offers a full array of services to assist scientific investigators in their work. They include:

- **Computer Bibliographic Services** - Technical specialists perform computerized literature searches and compile bibliographies upon request. The staff is experienced in retrieving citations and abstracts from some 155 scientific databases. (Request from Reference and Bibliographic Services.)
- **Current Awareness Service** - The Library's Selective Dissemination of Information (SDI) program provides users with regular computer updates on new literature in the biological and medical sciences. (Request from Reference and Bibliographic Services.)
- **Reference Services** - Reference librarians not only answer reference questions on site or by telephone (496-2184) but also advise users of other library services that may meet their needs.
- **Photocopying** - Copy machines are available to users in a self-service area. (Photocopy Service, lower level.) The library also will locate and copy articles upon request. (Request form at Circulation Desk.)
- **Microfilm and Microfiche** - Many journals are also kept in microform. Most are backfiles of important titles, acquired in order to save space. Reader-printers are reached through the Photocopy Service.
- **Circulation** - Books other than reference works and noncirculating reserve items can be checked out. Second copies of some of the most popular journals are also available for circulation.
- **Interlibrary Loans** - Research publications not in the collection can be obtained from other libraries. Photocopies of journal articles obtained from the National Library of Medicine are usually provided in one to two workdays.
- **Advisory Service to NIH Branches and Laboratories** - Staff of the Library will advise on organization and maintenance of office collections and on development of computerized search capabilities. (Request from Chief, Reference and Bibliographic Service Section.)
- **Translations** - Foreign language scientific materials are translated upon request from NIH staff. All translations are made availale to other users.
- **Stacks Service** - Library staff will search for any volume a user cannot find on the shelves. (Request form at Circulation Desk.)
- **Publications** - "Recent Additions to the NIH Library" is available monthly in printed form. "Current and Noncurrent Journals: NIH Library" is published biannually. Copies are available from the Circulation Desk.
- **Library Tours** - A tour providing an overview of NIH Library services and policies is available every Wednesday at 2 p.m., beginning from the Reference Assistance Desk.
- **Carrels** - Private study carrels are available on a limited, first-come basis. (Circulation Unit.)
- **Instruction** - Instruction on the use of the NIH Library and the automated catalog is offered periodically. "MEDLINE for the Health Professional" is taught monthly. (Further information is available from Reference and Bibliographic Services.) Staff will also give laboratory tutorials in MEDLINE.
- **"NIH Library . . . in Brief"** - This eight-page Library guide is available upon request at the Circulation Desk.
- **Information sheets** - One-page information sheets on specific services are available at the Circulation Desk.

Don Jones has supervised each of the MAPB Photography Section's two units: laboratory (1975-83) and camera (1983-88). He joined the Section in 1956 as a laboratory technician, and later transferred to photomacrography in the Camera Unit.

Medical Arts and Photography Branch

Ronald B. Winterrowd, Chief

The Medical Arts and Photography Branch is a central service organization which provides a wide variety of visual communication services to the NIH community. MAPB's products and services visually document scientific data, research programs and accomplishments for use in publications and presentations to the worldwide scientific community and the general public.

The Branch is staffed by professional artists, photographers, and other specialists who are experts in converting data into effective visual presentations. Their talents and skills are challenged daily in meeting the needs of scientists for graphic presentation, medical arts, photography (including photomacrography and photomicrography) and video production. Services include design and production of publications, preparation of slides, vugraphs, and other projected visual aids, exhibit design, statistical drafting, display charts, posters, medical illustrations, video recording, and support for special events.

The Branch's longstanding philosophy is to provide high quality professional services competitive in cost with commercially obtainable services. The staff works closely with private sector vendors of design, graphics and photography services to ensure that MAPB's quality standards are maintained.

During FY 88, MAPB continued to successfully meet the NIH community's constant and heavy demand for services. In-house services were again supplemented by the coordination of job requests with a wide variety of small business in the Washington metropolitan area. Competition among qualified vendors and daily bid sessions continued to ensure cost effectiveness while maintaining quality.

Major projects continued to reflect the emphasis on public education and prevention of health problems. Computer equipment was acquired in support of computer graphics services and publication design. Testing of various electronic imaging equipment for photomicrography was also performed.

During the year, MAPB underwent an evaluability assessment by an outside contractor. The study focused on the Branch's mission, organizational structure, and services; its specific goals were to determine if NIH's needs were being met, identify possible program management improvements, and provide recommendations for future program development. A comprehensive report will be forthcoming in early FY 89.

The Branch continued to offer its users an opportunity for information exchange through either the MAPB Advisory Committee or a staff team which is available to visit laboratories and offices to explain MAPB services, offer cost-saving suggestions, and invite recommendations on how MAPB services can be improved.

Photography Section

The Photography Section provided central photographic services to the NIH community including general (information), patient and surgical photography, photomicrography and photomacrography; and photographic laboratory processing. In order to accommodate the constant high volume of requests for laboratory services, the section continued to use private photographic facilities in the Washington area.

In FY 88, the Section was involved in the testing of digitally enhanced electronic imaging for photomicrography. During this effort, positive results were received from the research community because of the equipment's ability to capture extremely low light level fluorescence, digitize, and improve image clarity at both low and high power magnification.

In addition, a new patient photography studio has been designed for space identified on the first floor of the ACRF. This location will ease both inpatient and outpatient access and provide a safer, more attractive, and functional environment, with nearby medical personnel in case of an emergency situation. The updated studio facility will also improve the quality and consistency of patient photography.

Design Section

The Design Section employs graphic designers and illustrators to provide various design services to the NIH community. Many of these skilled and experienced designers have won awards in local, national, and international competitions. The Section provides publication design for public information, scientific presentations, poster design, editorial and technical illustrations, or whatever else may be required to support the research effort of the NIH. The Section also designs and produces support materials for conferences held at NIH.

In FY 88, the Section continued to experience a high demand for services. A MAC II system was recently purchased which will streamline design and production of publications and posters. Staff training has begun, and this service should be available to requestors in early FY 89.

Graphics Section

The Graphics Section's two units are composed of professionally trained, highly skilled and experienced illustrators, visual information specialists, exhibit specialists and TV production specialists.

The Graphics Unit continued to provide illustrations, charts, graphs, tables, slides, computer generated graphics, and other materials for scientific publications and presentations at meetings. The volume of requests remained high. Daily bid sessions continued to reduce costs to our clients through vendor competition.

During this year, the unit acquired the MacIntosh computer graphics system for in-house production of charts, graphs, text slides, etc. Staff training has been completed, and samples of artwork produced using the system are available in the reception area for interested clients.

The Special Events Unit continued to provide support for unusual or one-time events including poster sessions; exhibit design and fabrication; medical and scientific videotaping, editing and duplicating; Congressional and VIP presentations; Medicine for the Layman lectures; signage system design and production; and other special requests. The volume of requests continued to increase for poster sessions and video services.

The resources of the Video Unit of the Audiovisual Section, Travel and Administrative Services Branch, ORS, were transferred to the Special Events Unit early in FY 88. The move consolidates and expands video services within MAPB.

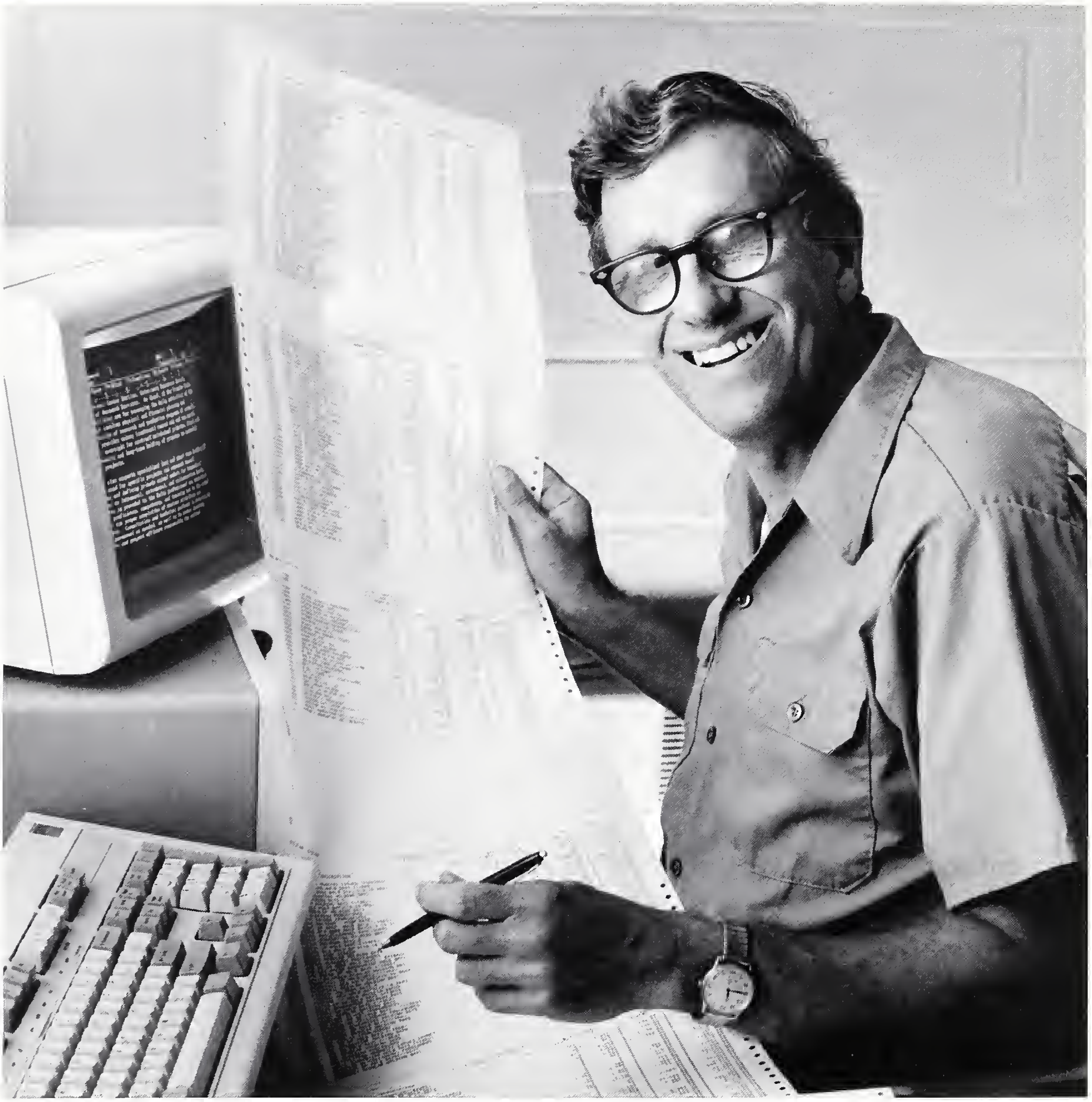
Medical Illustration Section

The Medical Illustration Section produced a wide variety of black-and-white and color medical illustrations and diagrams of surgical, gross pathological, ophthalmological, biological, and dental subjects. During FY 88 the Section continued its participation in public information projects, with medical illustrations used in poster designs, public information brochures, exhibits, and newsletters. Preliminary work was also begun on a long-term project for NCI involving illustrations for the Atlas on Oncologic Surgical Techniques.

Outlook for FY 89

MAPB will continue to provide the NIH community with the highest quality service at the lowest possible cost through competition among MAPB vendors, increased in-house productivity, and informing clients of ways they can reduce costs for job requests.

MAPB's evaluation study report will be reviewed. Planning for implementation of recommendations for management improvement, responsiveness, productivity, and efficiency will be initiated.



Bob Wolfes began work in the Veterinary Resources Branch (then called Laboratory Aids Branch) in 1958. He moved from the Bethesda campus to the NIH Animal Center, Poolesville, in 1964, when many buildings there were still uncompleted. Bob's many and varied responsibilities range from tours for visitors to preparing billing records of the Center's services to investigators.

Veterinary Resources Branch

Stephen Potkay, V.M.D., Chief

The Veterinary Resources Branch (VRB) provides professional and technical support service for NIH intramural programs. It is responsible for:

- Housing research primates, cats, dogs, rodents, and livestock
- Coordinating management and providing technical support for research projects conducted with animals housed in VRB facilities
- Procuring, quarantining, conditioning, and issuing animals from outside sources
- Diagnosing and controlling animal diseases
- Producing defined research animals
- Managing central animal surgery and radiology facilities
- Maintaining an international Laboratory Animal Genetic Resource
- Providing consultative services on animal health, care, husbandry, genetics, and nutrition

The Branch met these responsibilities and extended its efforts in assessing its services and their utility to NIH. This assessment was based on feedback from users of Branch services and from managers of institute research animal programs. The trend in the services requested has been toward the increased utilization of Branch facilities to house animals for intramural scientists while they conduct research projects and to provide additional space in which the scientists can work. Since Branch facilities were designed primarily for animal production and research holding, extensive renovations in several buildings have been required to create adequate investigator work space. Additional temporary space requirements, of both aforementioned types, were generated by the renovation of institute animal facilities to bring them into compliance with physical standards stated in the "Guide for the Care and Use of Laboratory Animals." The need to comply with "Guide" standards relates to the declared intent of the NIH to achieve accreditability by the American Association for Accreditation of Laboratory Animal Care (AAALAC) for all intramural animal care and use programs. Progress continued on plans to renovate space in one VRB building and undertake new construction nearby so as to meet requirements for a shared primate behavioral research laboratory. Renovations are also planned to accommodate a transgenic rodent activity for the National Cancer Institute (NCI) and to provide a holding area for rabbits and rodents used in institute research projects. Animals currently housed in the building will be moved into a recently modernized facility to house the NIH Animal Genetic Resource (NIHAGR) and the associated Embryo Cryopreservation Program. Additional building renovations were begun to upgrade their physical condition in order to maintain the AAALAC accredited status of the Branch animal care and use program. Plans for constructing a new facility at the NIH Animal Center were brought forward to provide high quality space for the centralized management of swine which are used in organ and bone marrow transplantation studies. The long-standing requirement for such was magnified by recent increases in NIH's use of dogs and the resultant need for the existing dog holding space which is now being used to house swine.

In addition to the efforts that have been made to renovate or plan new animal holding space to meet accreditation standards, considerable effort has been expended by VRB personnel towards upgrading the total NIH animal care and use program. Those efforts were exemplified by assistance with (1) developing, through the NIH Office for Animal Care and Use (OACU), a plan for moving institute animal care and use programs to an accreditable level, (2) the presentation of training programs for scientists and their technical assistants, and (3) developing plans for expanding centralized management of veterinary support services provided by the Branch. An important element in the improvement of the NIH program is the construction of an animal facility that will centralize the holding of animals which are currently located throughout the Clinical Center (CC). A contract was prepared to provide animal care and cagewashing services in the facility. Additionally, orders were placed for much of the new equipment that will be needed to support the wide variety of research to be conducted by those investigators who will relocate in this facility.

Animal Center Section

The Animal Center Section supplies, maintains, and develops large laboratory animals for use as models of human disease and provides related services and products for NIH investigators. The animals involved are mainly primates, farm animals, dogs and cats. Veterinary support and services are provided to intramural investigators who utilize these animals at the Animal Center or who require animal by-products such as blood and serums.

Primate Unit. The Primate Unit continued to provide services related to long-term holding, support for short-term projects and the procurement and quarantine of nonhuman primates. Approximately 330 primates were issued in FY 88 (Figure 1). In order to reduce maintenance costs, "pools" of monkeys were no longer kept on hand for immediate use. Rather, investigators requested animals in advance and purchased them when received by the Unit. They were made available to the investigator at the completion of the quarantine period. The Unit's average nonhuman primate inventory is expected to remain at about 1000.

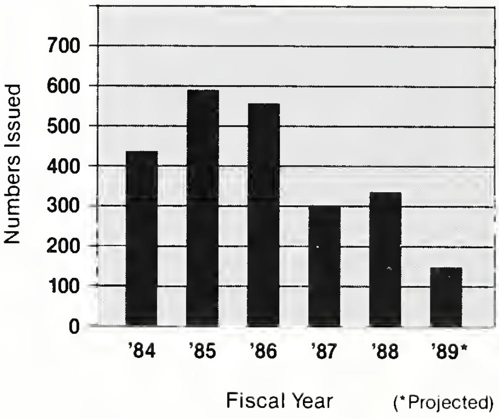


Figure 1
Numbers of Nonhuman Primates Issued

The need for quality rhesus (*Macaca mulatta*) monkeys in the 3 to 7 kg weight range has been met through procurement from Chinese sources. For this reason, and for cost considerations, the Primate Research Institute's breeding colony will cease to be a source for this species.

A variety of research projects conducted by scientists in the intramural program were supported as were several projects which involve other agencies such as the Department of Defense and the National Aeronautics and Space Administration (NASA). Inter- and intra-agency agreements were used routinely to assist with the financial management of projects requiring special arrangements for housing and to maintain animals on study. A study utilizing the rhesus monkey as a model to develop therapeutic regimens for preeclampsia was initiated in collaboration with the Virginia Polytechnical Institute. Pilot studies undertaken by the National Institute on Aging (NIA) to determine the effects of dietary restriction on longevity in rhesus and squirrel (*Saimiri sp*) monkeys were expanded to include more animals and modified to provide psychological enrichment for them. Other ongoing collaborative projects included an NICHD study of behavior and vocalization in squirrel monkeys and marmosets (*Callithrix jacchus*) as they relate to human development and a National Institute of Mental Health (NIMH)/National Institute for Child Health and Human Development (NICHD) project to determine the role of light on reproduction and molting in nonhuman primates. Simian AIDS (SAIDS) was the continued subject of investigation by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and DRS, utilizing macaques maintained in a closed environment.

A collaborative effort directed towards improving the psychological well-being of caged primates was initiated by DRS, NIMH, and OACU. Several large cages, designed to accommodate groups or families of primates and modified to permit manipulation and observation of the occupants, were ordered. Another type of environmental enhancement consisted of installing mirrors in several animal rooms to allow visual contact between individually caged animals. Experience with the caging and visual systems will provide a basis to evaluate them for potential use in other NIH facilities.

Carnivore Unit. A contract to purchase purpose-bred beagles and foxhound-type dogs was awarded in late FY 88 to meet the expected increase in demand for dogs next year. Dogs are presently being bred on a small scale for the purpose of maintaining estrous cyclicity and ovulation in the bitches. The breeding of naturally nervous pointers for NIMH has been temporarily discontinued, but research using them will continue. Breeding is expected to be resumed after further investigation of the colony's genetic characteristics.

In collaboration with the Uniformed Services University of the Health Sciences (USUHS), a study involving estrous induction in anestrous beagle and foxhound bitches was implemented. A number of collaborative projects with the National Zoo and USUHS were continued or newly established. Factors influencing fertilization and embryo development in the domestic cat were studied, and research involving the *in vitro* evaluation of embryo development in various feline species was initiated. This has significant implications for the propagation of difficult-to-breed or threatened species.

The National Eye Institute's (NEI) diabetes research project which utilizes beagles continues to progress. Treatment regimens have been developed as have methods for obtaining pathologic and ophthalmologic data. The duration of this study has been extended for several years because of the highly significant data that have been generated.

Ungulate Unit. The use of lambs and sheep by the National Heart, Lung and Blood Institute (NHLBI) was sporadic, largely because of non-availability and budgetary considerations, and the future of programs using this species is uncertain. It is anticipated, however, that the use of normal sheep blood will increase. The Ungulate Unit will supply this product from its donor flock.

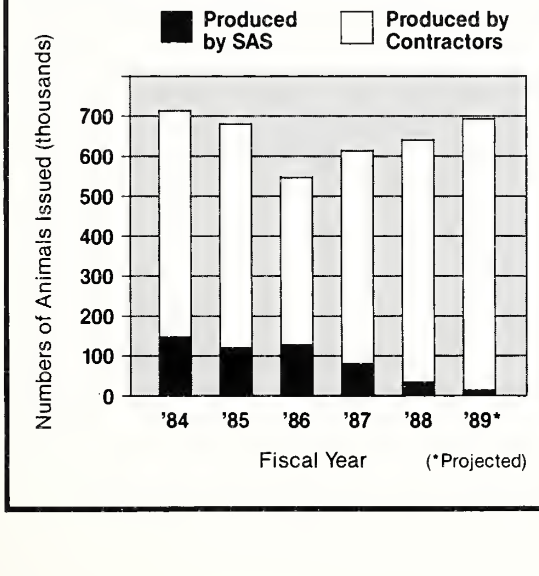
The SLA inbred miniature pig herd was redesignated by the NCI as the NIH mini pig. The size of the herd will probably continue to grow with the addition of genetic recombinants to the breeding herd. Changes in breeding management resulted in increased efficiency and an increase in the number of pigs born. Studies to determine the effects of long-term administration of progesterone on cystic endometrial hyperplasia (CEH) in the NIH mini pig continued, as did efforts to establish a flock of sheep homozygous for hyperbilirubinemia.

Small Animal Section

The Small Animal Section provides rodents and rabbits to the NIH intramural program through its in-house and contract production programs. It also manages the NIH Animal Genetic Resource (NIHAGR), a research animal holding activity, and programs in animal nutrition, model development, health and embryo cryopreservation.

Approximately 644,000 rodents and rabbits were issued through the Section in FY88 (Figure 2). Of these, 32,000 were from the Section's production colonies and 612,000 were from contract sources. Contracts included nine of the indefinite delivery type with commercial breeders and one research contract with the Division of Cancer Treatment (DCT), NCI. Animals from all sources were periodically monitored for pathogenic organisms.

Figure 2
Numbers of Rodents and Rabbits Provided by The Small Animal Section (SAS)



Genetic Resource. The NIHAGR consisted of about 300 closed breeding groups of mice, rats, guinea pigs, hamsters, rabbits, and cotton rats representing inbred, recombinant inbred, and congenic strains, and outbred and mutant stocks. The composition of the resource changed only slightly during the year. One new mouse strain, RFM/UN was introduced; one mouse mutant (Bronx Waltzer (*bv*)) and one guinea pig mutant (cataractous) were established. While there were many animal model projects awaiting development as well as an increasing number of requests for the production of animals maintained in the NIHAGR, these activities continued to depend on completion of facility renovations in Building 14F to provide the space in which to conduct them.

Reorganization within the Section directed towards combining the existing gnotobiotics, production and embryo cryopreservation activities into a single administrative entity was deferred pending a management analysis survey of broader scope.

Embryo Cryopreservation. The Embryo Cryopreservation Program was involved in studying the development and cryobiology of mouse embryos for the ultimate purpose of improving long-term cryostorage of valuable genetic material managed within the NIHAGR. Since 1984, more than 137,000 mouse embryos were collected, and about 35,000 were permanently stored. The remainder was used in comparative biological studies. A minimum of 1000 embryos has been permanently stored from each of 35 genotypes in the NIHAGR; more than 34,500 embryos were also collected from 29 stocks and strains of mice in FY88. Over 11,500 were cryopreserved, including 4,699 embryos from 17 genotypes, and added to the embryo bank. Continued emphasis was placed on utilizing embryo transfer procedures in mice to routinely produce live pups. To this end, the transfer of embryos from 20 donor genotypes into 200 recipient females was accomplished. The embryos were thawed, cultured *in vitro* for 24 hours, and transferred surgically into the uteri of pseudopregnant females. Using these methods, 49% of the recipients became pregnant and 25% of the total number of embryos transferred resulted in term pups. For each of the 20 donor genotypes, a minimum of 1 live pup was born during the year. While the pregnancy rate was similar to that obtained last year (52%), the proportion of transferred embryos that resulted in pups was improved. These results indicate that the overall transfer efficiency is increasing. During FY 1989, it will be determined if the site of embryo transfer can affect their subsequent *in vivo* maintenance.

Work was reinstated on rabbit embryo cryopreservation. Various freezing regimens were examined for their ability to support post-thaw survival of embryos at various stages of development. It was found that following preservation of morula stage embryos using a process of vitrification, post-thaw survival (75%) was superior to that obtained using conventional freezing methods (13%).

Research was undertaken in conjunction with NCI to develop cryopreservation techniques applicable to wild species of the genus *Mus* from both domestic and international sources with a view towards incorporating them into the NIHAGR and making them available to the biomedical research community at large.

Nutrition. There were no reports of problems associated with the quality of the NIH animal diets during the past year. A persistent problem associated with diets manufactured by extrusion, however, was the seepage of fat through the bags. A large percentage of the fat is sprayed on the outside of the biscuits and tends to melt when subjected to high temperatures. The use of thicker bags may be required to avoid this problem. Diet was implicated in the soft tissue calcification reported in guinea pigs used in long-term studies. Since most laboratory animal diets available at NIH were formulated for maximum growth or reproduction, many of the nutrient concentrations are in excess of those required for animal maintenance. There is a critical need for studies to ascertain their nutrient requirements for the maintenance of various laboratory animal species if they are to be involved in long-term studies.

The nutrition program continues to provide coordination in efforts to supply the biomedical research community with adequate numbers of Watanabe Heritable Hyperlipidemic rabbit. The Small Animal Section is currently the only domestic source of this rabbit. Its reproductive performance during 1988 was adequate to produce sufficient numbers of animals to meet the requirements of the noncommercial biomedical research community. However, the demand is expanding, and it may be necessary to develop a contract to produce larger numbers of this rabbit.

Research activities by individuals associated with the animal nutrition program included collaborative studies with BID scientists and researchers from other institutions involved with biomedical research. Major studies continued with scientists from the NIA, the National Institute of Environmental Health Sciences (NIEHS), Georgetown University, and NASA.

Program participation continued in the activities of the NIH Nutrition Coordinating Committee and its Subcommittee on Nutrition Education, where work on the Surgeon General's report on Nutrition and Health was completed during the year.

Animal Health. Infections with Theiler's mouse encephalomyelitis virus (TMEV/GDVII) and pneumonia virus of mice (PVM) persisted in 1988 and continued to be of concern. GDVII infections have not been associated with clinical signs, and its elimination, along with PVM, will be accomplished utilizing embryo transfer technology when the colonies are moved into the new barrier.

Research Support. The Research Support Unit held rodents and rabbits in the Research Holding facility and provided technical and professional support for ninety-four investigators from twelve institutes, the CC, and Food and Drug Administration (FDA). Animal holding increased by 27% as compared to 1987. The gnotobiotics activity quarantined a variety of animals and provided germfree animals to the NIHAGR barrier, contractors, and the biomedical research community.

Veterinary Medicine and Surgery Section

The Veterinary Medicine and Surgery Section maintains centralized facilities for large research animal holding and experimental surgery. It also provides routine care and comprehensive veterinary support for animals housed in the facilities. Section personnel provide consultations and direct assistance for NIH investigators, assist with the development of animal models for intramural research, and support active projects utilizing animals.

Surgery Unit. The Surgery Unit offers expertise and an optimal environment for aseptic surgical research. It handled about 1690 cases this year compared to about 900 the year before because of the support given to the NCI for bone marrow, kidney transplantation, and intraoperative radiation therapy work (Figure 3). A substantial amount of support has also been provided for NHLBI investigators who are working on a variety of projects related to the function of the cardiovascular system/functions.

Comparative Medicine Unit. The Comparative Medicine Unit provides centralized animal holding, veterinary care and consultation, and technical support to projects from ten different institutes at NIH. These projects involved the use of dogs, cats, sheep, miniature swine, ducks, and chickens. Numerous short-term and long-term projects were supported.

NCI remains a major user of the Unit's services. Miniature swine are being used as models for bone marrow and other organ transplantation studies, and significant numbers require intensive postoperative care. There will be a continued, if not expanded, need to

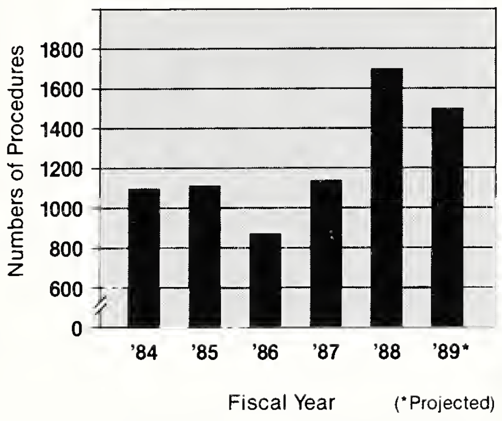


Figure 3
Surgical Procedures Performed

support swine used in the kidney transplantation portion of the project. A second NCI project involves the use of dogs to investigate the long-term effects of radiation therapy on vascular grafts and other tissues; this study will also be supported in the Unit. Another major component of animal holding space and technical support were devoted to a project for CC scientists using beagles as models to determine the pathogenesis of septic shock and to evaluate various treatment modalities. The Surgery Branch of the NHLBI continues to use approximately 200 sheep per year as surgical models for cardiovascular disease studies. Foxhounds are also being used by the NHLBI to study myocardial angiogenesis. The National Institute of Allergy and Infectious Diseases (NIAID) began a new study that has resulted in a significant commitment of the Unit's technical and caretaking staff. This study investigates the feline T-lymphotropic lentivirus as a model for HIV infection of man.

Major facility improvements completed in Building 28 included painting three animal wings and installing new monolythic floors. A new roof eliminated chronic leakage problems and permitted the completion of ceiling repairs. The building's electrical system was renovated: the number of outlets, safety features and available capacity were increased. Exhaust fans were added to help control the temperature in areas where animals that are particularly sensitive to heat are housed. A temporary structure was installed for feed and bedding storage. This made the current storage room available for testing a new laminar flow unit for housing immunosuppressed miniature swine.

Primate Research Unit. The Primate Research Unit housed an average population of 730 primates representing nine species for eight institutes, VRB, and CC. After renovations are completed, the total number of primates may increase by as much as 120-140 animals. Many are expected to come from Building 9 as part of the Building 14D prime project, but this project has been delayed significantly because of contract negotiations. The primate recycle program continued to operate at a low, variable level.

Ceiling and floor surfaces were under repair to bring the facility into compliance with the "Guide." Renovation of two rooms to accommodate baboons and equipped with new cages appropriate for housing primates weighing more than 15 kg were undertaken. The demand for technical support for projects in the Unit continued to increase.

Several cases of Simian Acquired Immunodeficiency Syndrome (SAIDS) were diagnosed this year, so the Unit will test groups of animals on a selective basis to begin the process of establishing a SAIDS-free population. Unit staff is participating on a committee to develop a policy which will guide the management of SAIDS-positive and suspect primates whenever they may be housed at NIH.

Comparative Pathology Section

The Comparative Pathology Section's mission is to characterize and improve the health status of laboratory animals and to study the naturally occurring diseases of those produced, quarantined, or utilized in biomedical research at the National Institutes of Health. It also monitors the genetic quality of NIH animals, which are used worldwide in research and testing. Laboratory animal disease diagnosis is performed by a staff of pathologists and microbiologists to aid in the control and elimination of disease in a wide variety of animals maintained in conventional, germfree, and barrier-sustained colonies. Research is conducted on the pathogenesis of naturally-occurring diseases of laboratory animals to facilitate both diagnosis and control of such diseases. Monitoring the genetic integrity of inbred mice is accomplished by testing for groups (profiles) of characteristics (markers) which identify the genetic constitution of each strain. Laboratory assistance, training and administrative liaison are provided for animal disease investigators and BID staff veterinarians concerned with control of diseases in NIH research laboratories. Importation and quarantine services are provided to permit the introduction of rodents and rodent products from non-approved sources into NIH while minimizing the risk of introducing ectromelia, lymphocytic choriomeningitis, and Hantaan viruses.

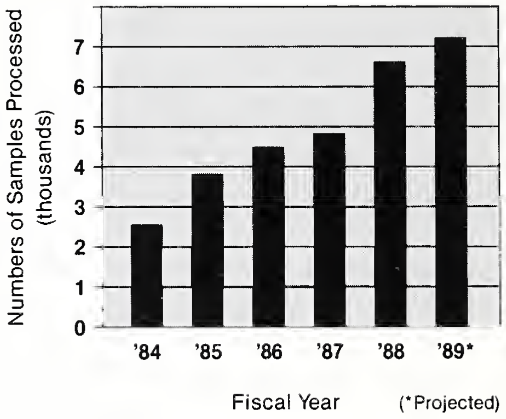
Section programs continued to change in order to accommodate new VRB/NIH activities. For example, the number of necropsies and the amount of work associated with them increased relative to overall increases in animal holding activities and changes in the nature of disease problems. Also, efforts continued to develop a coordinated NIH animal health surveillance program as will be required for AAALAC accreditation.

Pathology Unit. The number of necropsies performed by the pathology service was 3.1% more than last year. While the number of necropsies of animals from VRB colonies declined, the number of animals presented for necropsy by BID veterinarians increased greatly and will likely continue to increase. This reflects the BID veterinarians' continual reliance on CPS as a primary laboratory diagnostic service. Considerable assistance was given to investigators in distinguishing naturally occurring diseases from experimentally induced conditions, and substantial time was also devoted to consulting with clinicians and investigators in the diagnosis, control and prevention of animal diseases.

Deaths were caused by a variety of miscellaneous conditions. A number of guinea pigs and rabbits were stillborn (fetal atelectasis), and although cecitis in rabbits remained a significant problem, there were no massive outbreaks. Four hundred and two hamsters from one institute were necropsied during an outbreak of a proliferative ileitis-like/infectious lymphoma syndrome. The causative agent has not yet been identified; diagnostic work is continuing.

Microbiology Unit. The number of clinical pathology samples processed in FY 88 declined by about 16% from last year; the decrease resulted partly from a temporary decrease in monitoring of animals in the NIHAGR. During the year, the in-house rodent serology battery was expanded to include tests for GDVII, MVM, Reo3, ectromelia, LCM, and KRV/H-1. This allowed the majority of the rodent serology testing to be done in-house, and in-house testing now includes most of the important rodent viruses. It is anticipated that the serology workload will increase significantly with the completion of renovations to house the NIHAGR and the continued implementation of routine animal health monitoring programs on campus. The number of bacteriology samples processed increased by over 35% last year (Figure 4) because of an increase in the submission of non-necropsy specimens (swabs and fecal samples). This trend is expected to continue because of the expanded role that CPS will play in routine NIH animal health monitoring and the inclusion of limited environmental monitoring among CPS services. The bacteriology records are now incorporated into the computer database.

Figure 4
Numbers of Bacteriology Samples Processed



The Animal Disease Investigation (ADI) Service responded to 53% more calls than in FY 87 because of the previously described disease outbreak in hamsters and increased case submissions by the Institutes. The latter will undoubtedly continue as health monitoring needs are more fully identified in the Institutes.

The projected number of permits for introductions of rodents and rodent products from sources other than those approved by the Small Animal Section was 20.

Genetics Unit. Approximately 3000 animals from the NIHAGR and Production Colonies were received, and this number is expected to remain constant. The genetic monitoring program has undergone remarkable growth in the past few years and has changed to meet the needs of both the NIHAGR and NIH investigators. Currently, monitoring is applied to over 250 inbred lines on a routine basis, and monitoring the development of recombinant inbred and congenic lines of rodents constitutes a large proportion of the workload. This work assists in the development of the lines and ensures their genetic purity. Detailed genetic profiles also assist individual investigators in selecting the appropriate animal for use in their experiments.

No major genetic contaminations were reported or detected in any of the inbred lines maintained by the Small Animal Section. The Program responded to a number of requests from investigators to verify the genetic profiles of animals from colonies established with breeding pairs from the NIHAGR, and several intramural investigators requested testing of animals obtained from commercial sources. It is anticipated that the number of requests for assistance from the Genetic Investigation Service will remain constant at approximately 25 per year.

Research Activities. Research activities were concerned with studies of the pathogenesis of diseases occurring in the animal colonies, the control of such diseases, and the development of methods for monitoring infectious agents and genetic purity. Research conducted in FY 88 included studies of mouse strain susceptibility to *Bacillus piliformis* and the development of genetic profiles for inbred labortory rodents. Within manpower limitations and under appropriate circumstances, collaborative studies were carried out with BID investigators and occasionally with groups outside of NIH.

Forecast

All available animal housing space in VRB facilities is filled to near capacity, and the number of animals housed is not likely to change dramatically unless unforeseen changes occur in individual research programs. Additional space for animal housing and for investigator work areas is needed to accommodate expansions and new starts in animal-oriented intramural research. The Branch already has identified housing space shortages for nonhuman primates, rabbits, and rodents. Participation by Branch staff in a variety of activities supporting the upgrading of NIH animal programs will increase, because the institutes are looking to VRB to assume a leadership role in this function. That role will focus on the development and maintenance of state-of-the-art facilities and programs, in keeping with the stated goals of the NIH Director. Participation will include expanding existing services, such as animal health monitoring, to include all institute animal colonies and providing new services such as centralized cagewashing. Branch staff and other resources will also need to be expanded as the responsibility for centralized management of new animal facilities is shifted to VRB. Requests for more sophisticated technical support for research projects are also expected to increase and will require that more emphasis be placed on personnel training in VRB.